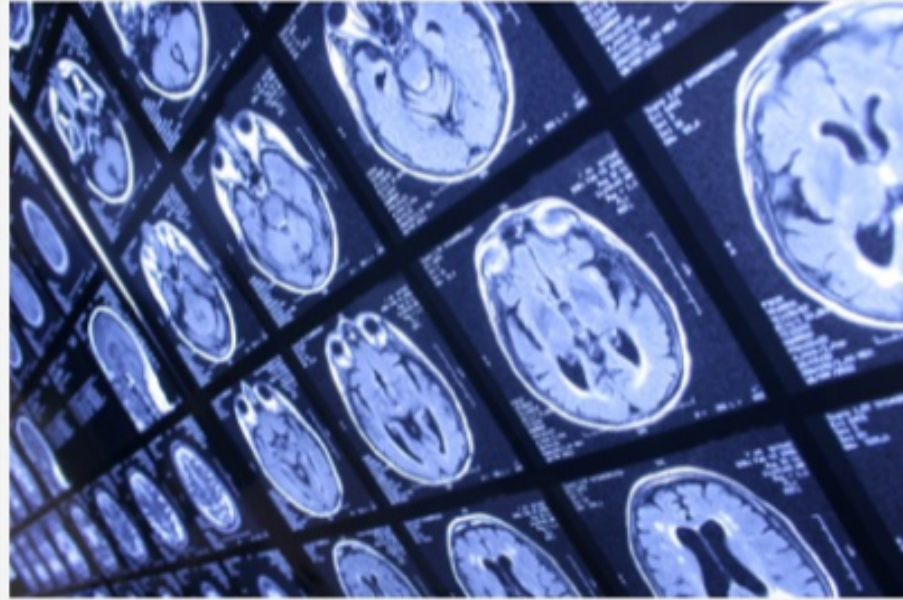


# Is the P-FIT it? Part 1—The P-FIT model described



At IM-HOME blog

[Note – this is the first in a series of posts intended to present an integration of intelligence, cognitive neuroscience, and applied neuroscience research with the goal to advance a set of hypotheses or model(s) that explain how the Interactive Metronome® (IM) technology results in improved cognitive functioning—specifically *focus or controlled attention*]

The *law of individual differences* is the only proven law in psychology. This law has resulted in decades of research regarding theories and models of intelligence and individual differences in intelligence. Within the past two decades a general consensus has emerged from the psychometric intelligence research that the **Cattell-Horn-Carroll (CHC) theory of intelligence** is the most empirically supported taxonomy for understanding the structure of human intelligence.

Although the CHC taxonomy provides a useful description and nomenclature for describing and measuring intelligence, it provides little guidance regarding the underlying brain mechanisms that account for differences in human intelligence. During the past few decades brain imaging research has started to map psychometric intelligence constructs (*g* or general intelligence, *Gc*-crystallized intelligence; *Gf*-fluid intelligence; *Gv*-visual-spatial processing; see **Colom, Haier, Head, Alvarez-Linera, Quiroga, Shih & Jung, 2009**) to brain structures and networks. In the context of applied neuroscience research, the law of individual differences is captured by the conclusion that “the brains of some people are more *efficient* than those of others” (**Deary, Penke & Johnson, 2010**, p. 210; emphasis added). This conclusion, based on structural and functional brain-imaging studies, is also consistent with the *neural efficiency hypothesis* of Jensen.

As discussed previously in a prior post (**Brain or neural efficiency: Is it quickness or timing?**):



The *neural efficiency hypothesis* states that the faster the brain's synapses fire the more efficient and faster the transmission of information within the brain, both at the level of individual nerve synapses and eventually at the level of fine-tuned communication across the various brain networks. Neural efficiency is not a thing or structure of the brain but an indicator of how well the brain is working. For example, in most cars the engine parts are generally the same. There is no "horsepower" part, but the collective synchronization of the various parts of the engine produce different levels of horsepower for different engines or the same engine under different conditions. In simple terms, neural efficiency is analogous to mental efficiency or horsepower. The neural efficiency hypothesis has been the dominant theory for explaining differences in general intelligence. It is associated with one of the most prominent intelligence scholars for decades, Dr. Arthur Jensen.

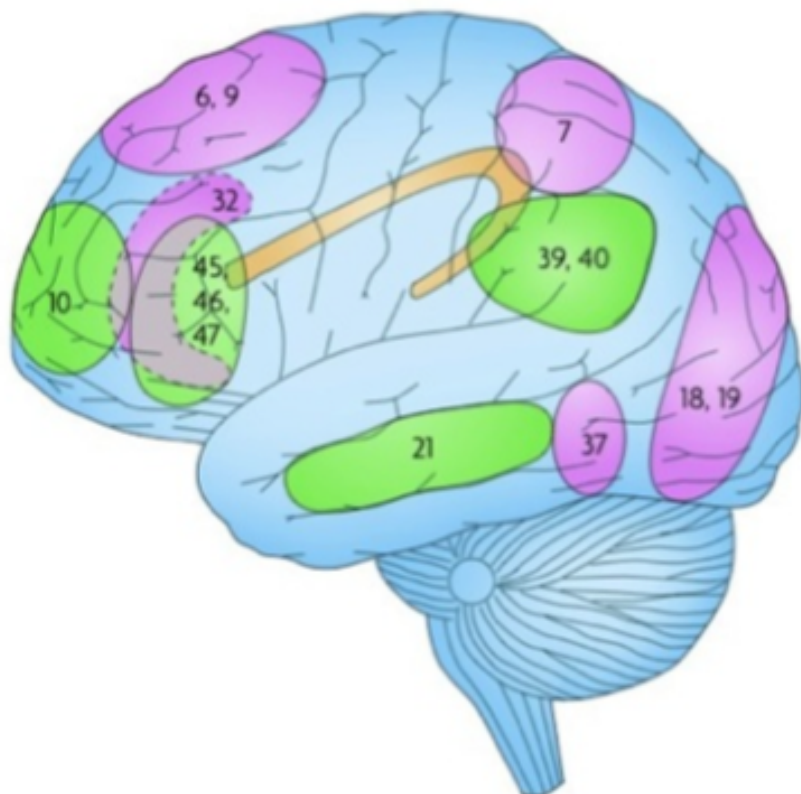
### The Parietal-Frontal Integration Theory (P-FIT)

Probably the most empirically-based neuroscience model of human intelligence to emerge is the *parietal-frontal integration theory (P-FIT)* advanced by Jung, Haier, Colom and colleagues (Colom et al., 2009; **Jung & Haier, 2007**). The *P-FIT* model is based on a synthesis of over three dozen brain imaging-psychometric intelligence research studies. These studies used a variety of brain imaging techniques such as structural and functional MRI, diffusion tensor MRI, magnetic resonance spectroscopy, and positron emission tomography studies (**Deary, 2012**).

The details and nuances of the *P-FIT* model of intelligence cannot be covered here. Interested readers should consult the work of Deary et al. (2010), Jung and Haier (2007) and Colom et al. (2009). The important conclusion to date is that this program of research has established *correlations between individual differences in general intelligence (g; and also the CHC domains of Gf, Gc and Gv) and certain core brain networks*. In particular, the model suggests that general intelligence, which has been related to the concept of neural efficiency, is primarily a function of the efficient flow of information between the dorsolateral prefrontal cortex, parietal lobe, anterior cingulate cortex and specific regions in the temporal and occipital cortices. [Figure from Deary et al., 2010]







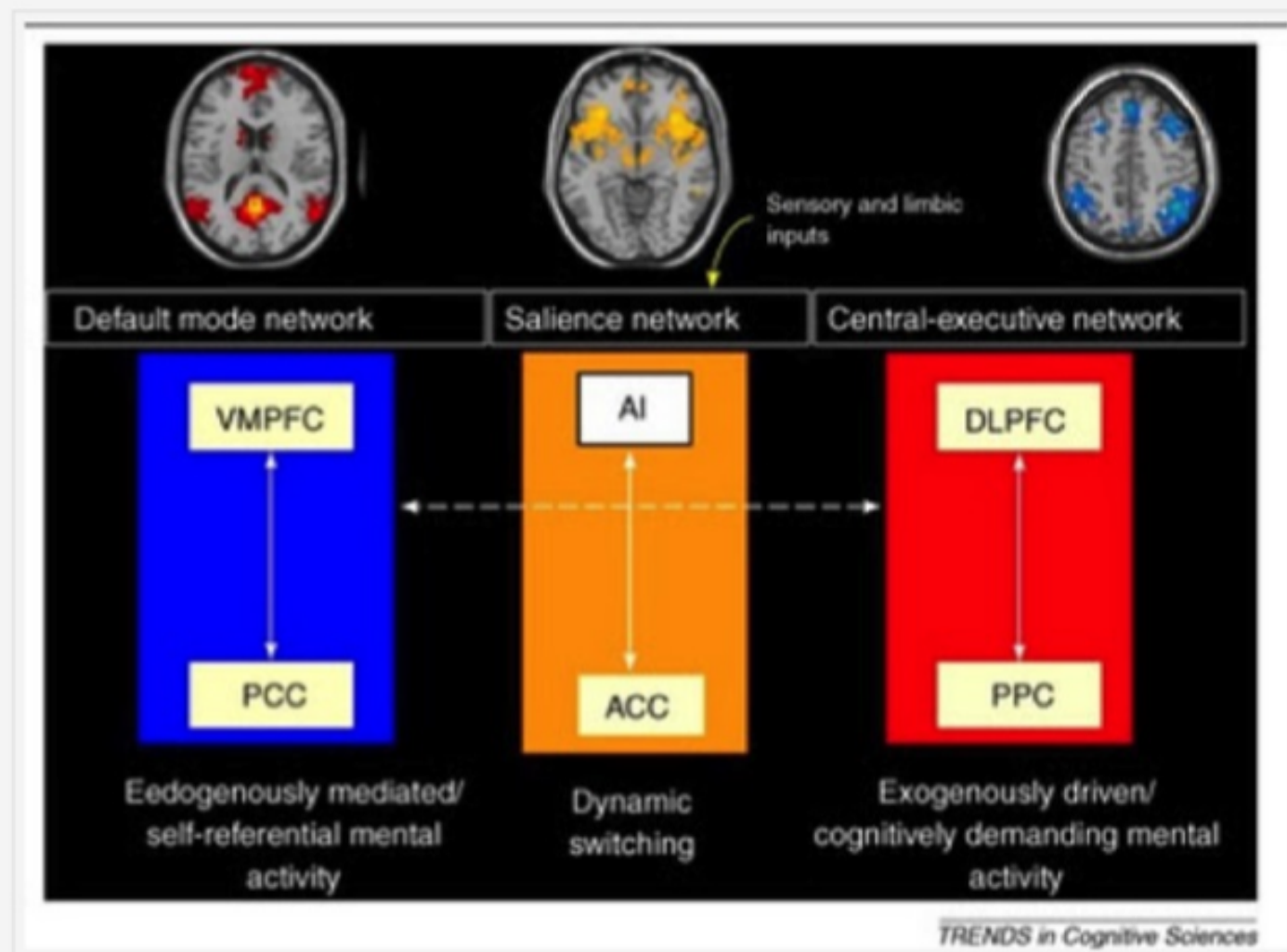
**Figure 2 | The loci of intelligence differences.** Based on a review of all the structural and functional neuroimaging literature that was available, Jung and Haier proposed the parieto-frontal integration theory of intelligence (P-FIT), which is arguably the best available description of how intelligence is distributed in the brain. The figure shows Brodmann Areas (BAs) involved in intelligence, as well as the arcuate fasciculus (shown in yellow) as a promising candidate for a white matter tract that connects the involved brain regions. BAs shown in green indicate predominantly left-hemispheric correlations and BAs shown in pink indicate predominantly right-hemispheric correlations with intelligence. Figure is modified, with permission, from REF. 60 © (2007) Cambridge University Press.

According to Deary et al. (2010), the “P-FIT can be considered the best available answer to the question of where in the brain intelligence resides” (p. 207). More importantly:

“There is an emerging consensus that intelligence does not reside in a single, narrowly circumscribed brain region such as the frontal lobe. Rather, *intelligence seems to be best described as a small-world network.* This model implies that high intelligence probably requires *undisrupted information transfer among the involved brain regions along white matter fibres*” (p. 207; emphasis added)



This conclusion is consistent with, and reinforces, the recent large-scale brain network research discussed in a prior post ([The brain as a set of networks: Can you fine-tune your brain?](#)). Of particular interest is the conclusion from large-scale brain network studies (see Bressler & Menon, 2010 in prior post) is that of the three primary identified networks (default, salience, central-executive), the central executive network “*is engaged in higher-order cognitive and attentional control.*” In other words, when you must engage your conscious brain to work on a problem, place information in your working memory as you think, focus your attention on a task or problem, etc., you are “thinking” and must focus your controlled attention. [Image from Bressler and Menon, 2010; see prior post link above].



The goal of this series is not to delve into complex brain function terminology or analysis of brain structures and networks. Future posts in the “*Is the P-FIT it?*” series will link the neuroscience-based *P-FIT* model of general intelligence with remarkably similar neurocognitive and neuroscience based research findings that account for the links between working memory and reasoning/general intelligence, ADHD, certain forms of meditation, and the pivotal role of *controlled executive attention* (aka, *focus*) in working memory—which, in turns, results in improved cognitive or intellectual performance.



# HUMAN INTELLIGENCE



2011

EARL HUNT



## 7.5. The Brain and Specific Cognitive Functions

Accepting the idea that the brain is a tool kit, we now look at some of the specialized tools. We first look at the relation between working memory and brain functions, on the grounds that working memory is tightly enmeshed with general reasoning, and hence our most important single general processing capacity. We then look at the brain structures underlying other information-processing capacities that have been associated with various aspects of intelligence.

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### 7.5.1. *The Brain and Working Memory: Evidence and the P-FIT Model*

Figure 7.3 summarizes the findings of over two hundred studies in which brain metabolism was measured as people did various activities related to attention and relatively short-term memory, including operations on information while it is being held in memory.<sup>28</sup> The reviewers summarized the study as showing that working memory tasks showed heavy involvement of the frontal and parietal cortices, and the anterior cingulate gyrus. Lateralization depends upon the

<sup>28</sup> Cabeza & Nyberg, 2004. See also Smith & Jonides, 1999.

nature of the stimuli. In general, problems involving spatial and figural stimuli produce greater activation in the right than in the left hemisphere, while the reverse pattern is seen for problems involving language.

Figure 7.3 shows what parts of the brain are involved in working memory tasks in general. But to what extent are these areas related to individual differences in intelligence, and especially to either (depending on your theoretical predilections) g or Gf? One approach to this question is to take tasks that are known to have high g loadings in the intelligence literature, such as progressive matrix tests, and to determine what areas of the brain are active when people do these tasks. Another strategy is to determine what sort of brain injuries result in selective loss of the ability to deal with Gf-type problems, as opposed to Gc-type problems, where the solution depends largely on retrieving previously acquired information.

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Both approaches lead to essentially the same answer.<sup>29</sup> Jung and Haier have





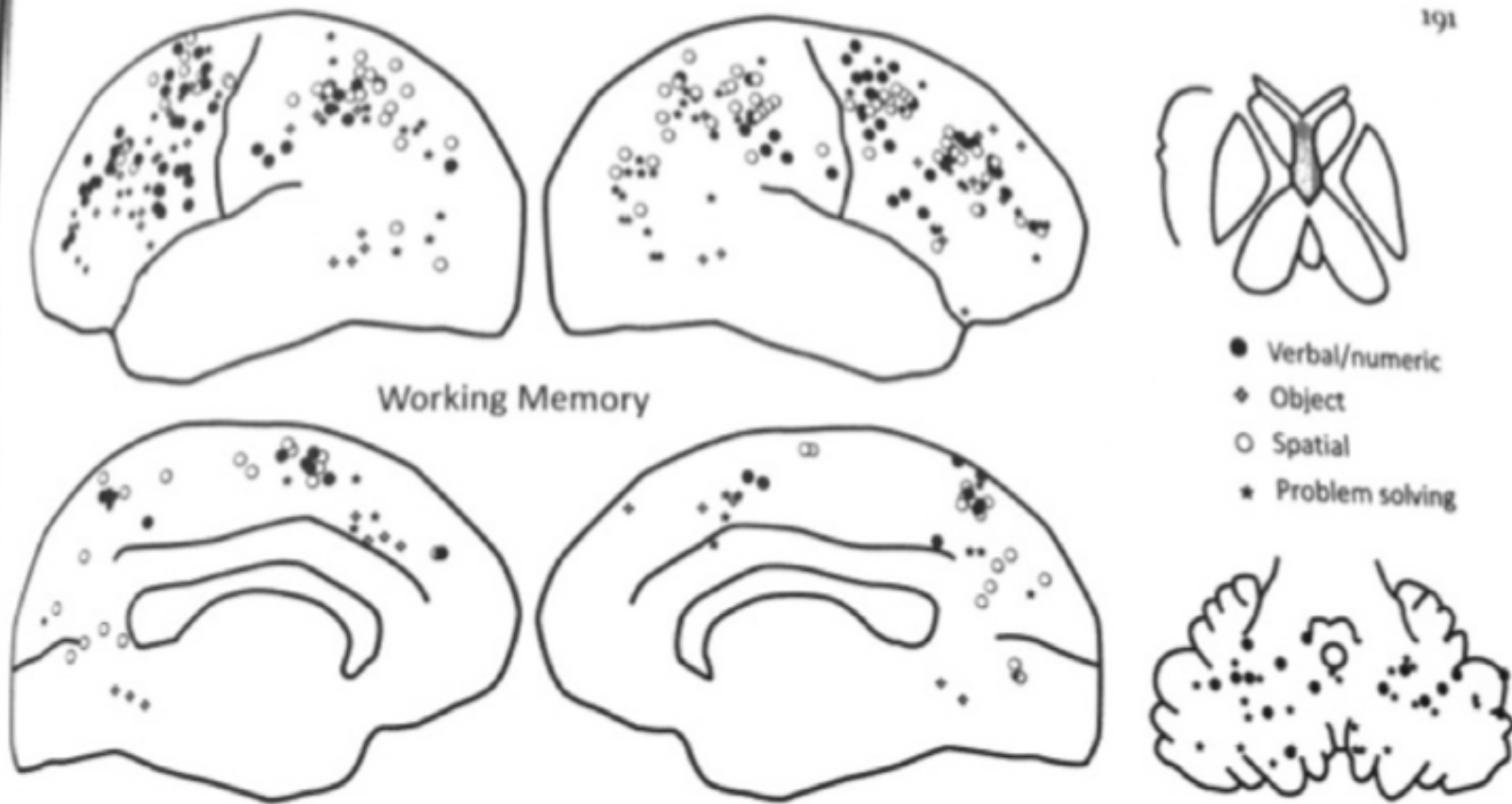


Figure 7.3. A sketch of areas of the brain that show activity during a variety of tasks involving working memory. The upper figures show a lateral view of the cortex; the lower figures show a medial view. From Cabeza & Nyberg, 2000, Figure 3. Reprinted with the permission of Massachusetts Institute of Technology Press Journals.

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produced the *Parieto-Frontal Integration Theory* (P-FIT) theoretical model that does a good job of encapsulating our present knowledge.<sup>30</sup> They propose that our ability to do the sort of thinking captured by measures of Gf and working memory is supported by a system of brain regions involving the dorso-lateral frontal cortex, the parietal lobe, and the anterior cingulate gyrus. Each of these regions performs some of the functions needed for abstract reasoning and problem solving; no one of them is sufficient alone.

Jung and Haier's idea of the role of the frontal cortex is consistent with other observations, both of imaging results and of the sort of scattered thinking displayed by Phineas Gage, and by many other patients with frontal lobe damage. In general, the frontal lobes seem to be necessary to keep a person on-task.<sup>31</sup> In one study that nicely

and Haier, White, & Alkire, 2003, for differential activation of brain areas during imaging; and Colom, Jung, & Haier, 2006, for a discussion of the relation between neural density and g loadings.

<sup>30</sup> Jung & Haier, 2007.

illustrates the effect, it was shown that children who did not have a history of attention disorder prior to injury to the frontal and especially prefrontal-cortex displayed symptoms of attention deficit disorder after the injury.<sup>32</sup> One of the intriguing findings on this topic is that one area of the frontal lobe appears to be responsible for orchestrating thinking about things and abstract ideas, while another region orchestrates thinking about socially relevant topics.<sup>33</sup>

Jung and Haier argue that the parietal cortex is responsible for integrating information from various sensory modalities. This would be consistent with the parietal cortex's established role in controlling the deployment of attention externally, to particular regions of and objects in the sensory fields.<sup>34</sup> The role of the parietal cortex in providing temporary storage areas for information also appears to be well established. This seems to be an area where the lateralization is especially well marked; linguistic information, the phonetic loop in Baddeley's model, resides in the left (in most of us), while spatial and object information is held on the right.<sup>35</sup>

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on the right.<sup>35</sup>

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Jung and Haier propose that the anterior cingulate gyrus acts as a response selection device. It is responsible for directing decisions, albeit with substantial regulatory input from the frontal lobes. The anterior cingulate gyrus also seems to weigh the likely consequences of taking an action. Clancy Blair, a developmental psychologist at Pennsylvania State University, has pointed out that recent research, which it would take us too far afield to examine, has shown that emotional evaluation of outcomes plays an important part in response selection, even in situations where one would expect rational decision making to be the norm.<sup>36</sup> Combining Blair and Jung and Haier's views, an important part of the frontal cortex-cingulate gyrus interaction

32 Max et al., 2005.

33 Beer, Shimamura, & Knight, 2004.

34 Posner et al., 2006.

35 Cabeza & Nyberg, 2000. For a good illustrative study, see Smith & Jonides, 1999.

36 Blair, 2006.



may be modulation of the emotional and nonemotional aspects of decision making.

In summary, there is clear evidence that the working memory system, which we know is central to reasoning and general intelligence, is supported by a brain system involving regions of the frontal lobe, the parietal lobe, and the anterior cingulate cortex. I do not want to give the impression that these are the only areas involved, or that all the details of the involvement have been worked out. They have not, but the outline is clear.

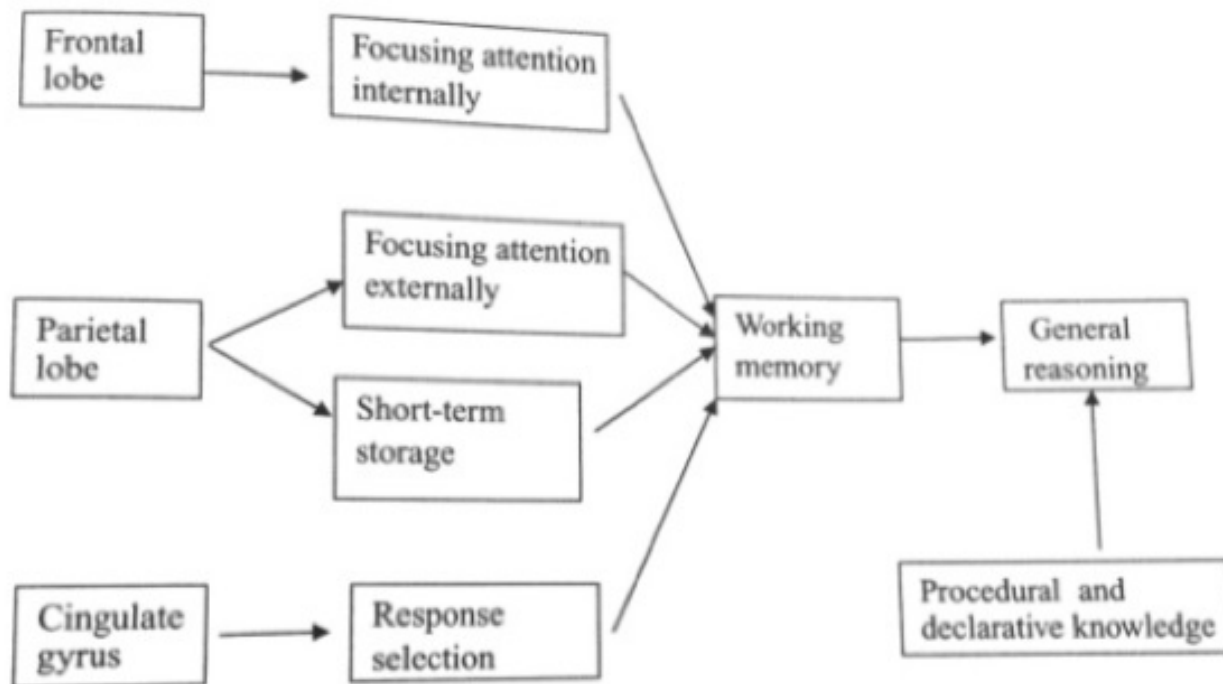
Behaviorally, g is virtually synonymous with general reasoning ability, which in turn is synonymous with individual differences in working memory. By this argument the seat of g is in the frontal-parietal-cingulate cortex system. However, this raises some problems. Vocabulary tests are highly g loaded, but tests involving syntactical and semantic analyses of single words do not activate the entire frontal-parietal-cingulate system, and do activate areas outside of this system, notably in the temporal lobe.<sup>58</sup> The source of g seems to jump around as the task changes. Why?

<sup>57</sup> Jensen, 1998, p. 74.

<sup>58</sup> See Figure 7.5. For a typical study, see Friederici, Opitz, & von Croman, 2000.







**Figure 7.9.** Hypothetical relationships between brain systems, narrowly defined information-processing functions, working memory, and general reasoning ability (*g*). This diagram is not proposed as a model, but rather to show the complexity of the issue, and the need to deal with broadly defined abilities, such as *g*, as emerging from a system of interacting components, rather than being a thing in itself.

## An integrative architecture for general intelligence and executive function revealed by lesion mapping

Aron K. Barbey,<sup>1,2,3,4,5</sup> Roberto Colom,<sup>6</sup> Jeffrey Solomon,<sup>7</sup> Frank Krueger,<sup>8</sup> Chad Forbes<sup>9</sup> and Jordan Grafman<sup>10</sup>

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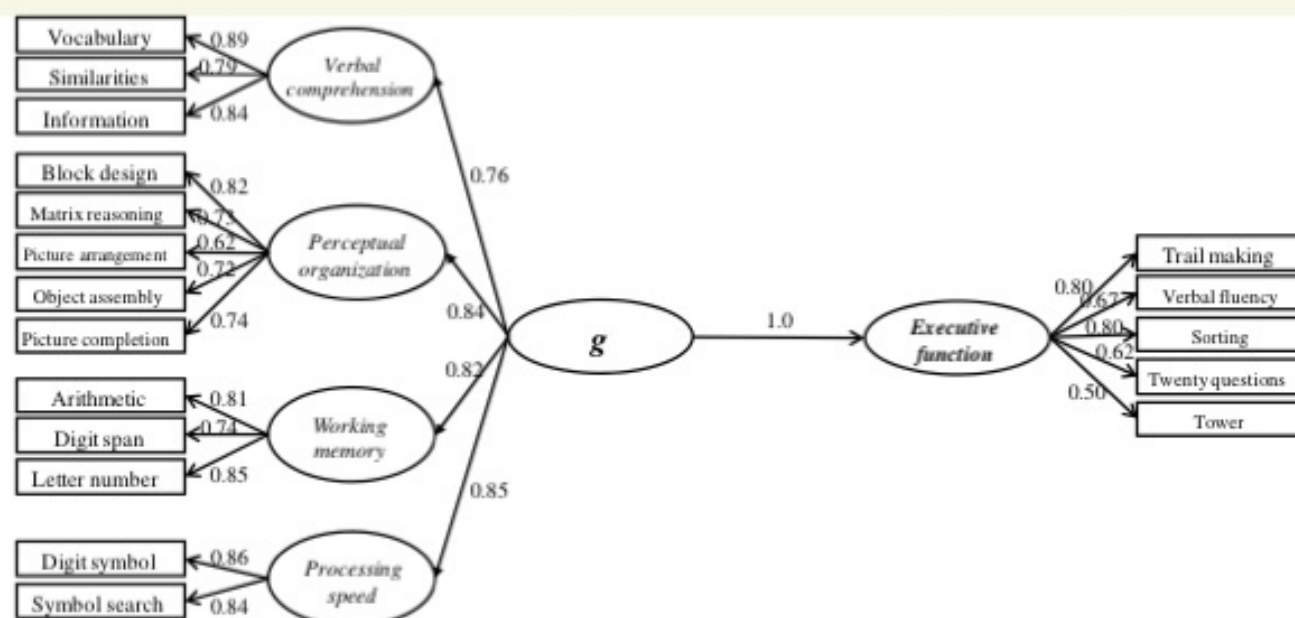
Although cognitive neuroscience has made remarkable progress in understanding the involvement of the prefrontal cortex in executive control, the broader functional networks that support high-level cognition and give rise to general intelligence remain to be well characterized. Here, we investigated the neural substrates of the general factor of intelligence (*g*) and executive function in 182 patients with focal brain damage using voxel-based lesion-symptom mapping. The Wechsler Adult Intelligence Scale and Delis-Kaplan Executive Function System were used to derive measures of *g* and executive function, respectively. Impaired performance on these measures was associated with damage to a distributed network of left lateralized brain areas, including regions of frontal and parietal cortex and white matter association tracts, which bind these areas into a coordinated system. The observed findings support an integrative framework for understanding the architecture of general intelligence and executive function, supporting their reliance upon a shared fronto-parietal network for the integration and control of cognitive representations and making specific recommendations for the application of the Wechsler Adult Intelligence Scale and Delis-Kaplan Executive Function System to the study of high-level cognition in health and disease.

**Keywords:** fronto-parietal network; general intelligence; executive function; voxel-based lesion-symptom mapping

**Abbreviations:** D-KEFS = Delis-Kaplan Executive Function System; WAIS = Wechsler Adult Intelligence Scale







**Figure 1** SEM analysis of the administered WAIS and D-KEFS measures.

average loading for the D-KEFS measures on this same factor was 0.59, which is consistent with their equivalent psychometric behaviour on the factor representing the shared common variance (see Colom *et al.*, 2006c for examples of re-analyses of several data sets using this hierarchical approach). The psychometric structure observed in the Vietnam Head Injury Study patient sample (Fig. 1) is similar to that of the WAIS standardization described by Taub (2001), providing evidence to further validate our assessment of psychometric *g* in this neuropsychological patient sample.

It is important to keep in mind that the factor structure obtained here is derived from the analysis of a clinical sample, raising the question of whether it resembles the obtained factor structure found for non-clinical samples. The available evidence supports the view that there is a close similarity. The factor structure of the Wechsler scales

Values between 0 and 0.05 indicate good fit, values between 0.05 and 0.08 represent acceptable errors and values  $>0.10$  are indicative of poor fit (Byrne, 1998). Finally, comparative fit index is also reported; acceptable values must be larger than 0.90 (Marsh *et al.*, 1988). The fit for this model was appropriate:  $\chi^2 (131) = 283$ ; CMIN/DF = 2.16; RMSEA = 0.08, comparative fit index = 0.921. Results indicate that within this model, psychometric variation in executive function is entirely explained by *g*, which is highly consistent with the correlation of 0.87 reported above between *g* and executive scores submitted to lesion analyses. This suggests that both psychological constructs depend largely on common cognitive operations and raises the intriguing possibility that these high-level processes may also recruit common neural machinery.



## Gray matter correlates of fluid, crystallized, and spatial intelligence: Testing the P-FIT model

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### ABSTRACT

The parieto-frontal integration theory (P-FIT) nominates several areas distributed throughout the brain as relevant for intelligence. This theory was derived from previously published studies using a variety of both imaging methods and tests of cognitive ability. Here we test this theory in a new sample of young healthy adults ( $N = 100$ ) using a psychometric battery tapping fluid, crystallized, and spatial intelligence factors. High resolution structural MRI scans (3T) were obtained and analyzed with Voxel-based Morphometry (VBM). The main findings are consistent with the P-FIT, supporting the view that general intelligence ( $g$ ) involves multiple cortical areas throughout the brain. Key regions include the dorsolateral prefrontal cortex, Broca's and Wernicke's areas, the somato-sensory association cortex, and the visual association cortex. Further, estimates of crystallized and spatial intelligence with  $g$  statistically removed, still share several brain areas with general intelligence, but also show some degree of uniqueness.

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Plomin, 2006), because several regions distributed across the entire cerebral cortex and within discrete white matter regions are identified. These P-FIT regions generally imply distinguishable information processing stages (Fig. 1):

1. In the first stage, temporal and occipital specific areas process sensory information: the extrastriate cortex (Brodmann areas –BAs– 18 and 19) and the fusiform gyrus (BA 37), involved with recognition, imagery and elaboration of visual inputs, as well as the Wernicke's area (BA 22) for analysis and elaboration of syntax of auditory information.
2. The second stage implicates integration and abstraction of this information by parietal BAs 39 (angular gyrus), 40 (supramarginal gyrus), and 7 (superior parietal lobule).
3. In the third stage, these parietal areas interact with the frontal lobes, which serve to problem solve, evaluate, and hypothesis test. Frontal BAs 6, 9, 10, 45, 46, and 47 are underscored by the theoretical model.
4. Finally, the anterior cingulate (BA 32) is implicated for response selection and inhibition of alternative responses, once the best solution is determined in the previous stage.

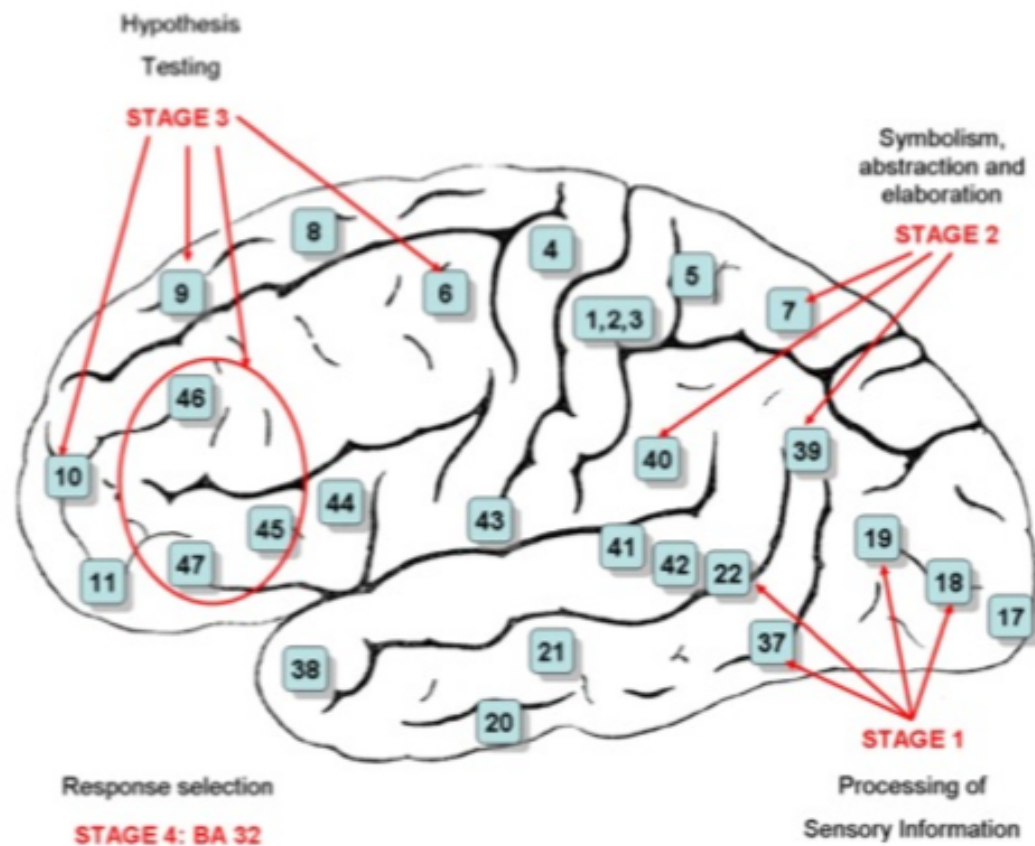
White matter (WM), especially the arcuate fasciculus, plays a critical role for a reliable communication of information across these brain processing units.

Jung and Haier (2007) posit that not all these brain areas are equally necessary in all individuals for intelligence. They predict that discrete brain regions of the dorsolateral prefrontal cortex (BAs 9, 45, 46, and 47) and the parietal cortex (BAs 7 and 40) may be key for the core of general intelligence.

Whereas the P-FIT stressed the commonalities among studies, Colom (2007) noted the great variability among the studies summarized by Jung and Haier (2007). Only a very small number of discrete brain areas approach 50% of convergence across published studies employing the same

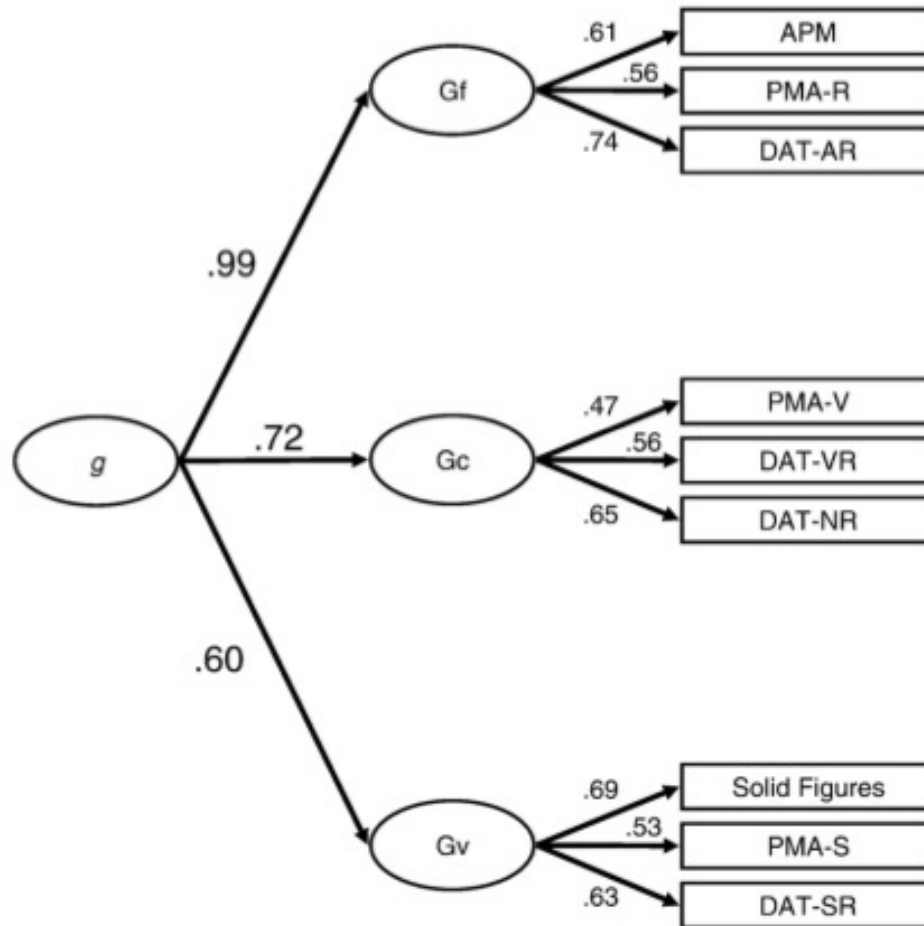






**Fig. 1.** Processing stages associated with specific brain regions according to the P-FIT model: processing of sensory information (stage 1), symbolism, abstraction and elaboration (stage 2), hypothesis testing (stage 3), and response selection (stage 4). The arcuate fasciculus (i.e. the neural pathway connecting the posterior of the temporo-parietal junction with the frontal cortex) is not shown in the figure, but also underscored by the P-FIT model.

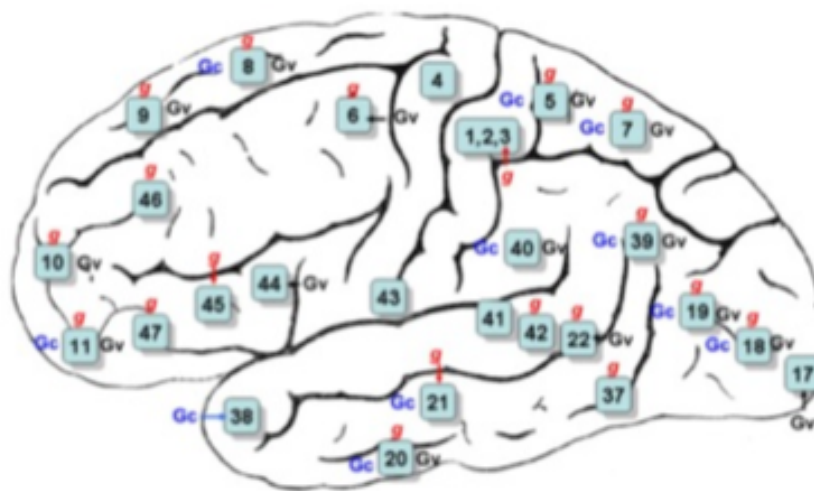




**Fig. 2.** CFA model for the considered psychometric measures of intelligence (APM = Advanced Progressive Matrices Test, PMA-R = inductive reasoning subtests from the PMA Battery, DAT-AR = abstract reasoning subtest from the DAT Battery, PMA-V = vocabulary subtests from the PMA Battery, DAT-VR = verbal reasoning subtest from the DAT Battery, DAT-NR = numerical reasoning subtest from the DAT Battery, PMA-S = mental rotation subtest from the PMA Battery, DAT-SR = spatial relations subtest from the DAT Battery). It can be seen that fluid intelligence (*Gf*) is perfectly predicted by the general intelligence higher-order factor (*g*).







**Fig. 6.** Overlapping and non-overlapping clusters for general (g), crystallized (Gc-r), and spatial intelligence (Gv-r). Overlapping clusters concentrate on BAs 8 and 11 (frontal lobe), BA 5, 7, and 39 (parietal lobe), BA 20 (temporal lobe), and BAs 18 and 19 (occipital lobe). Non-overlapping clusters for Gc are focused on BAs 45–47 (frontal lobe), BA 3 (parietal lobe), and BAs 37 and 42 (temporal lobe). The non-overlapping cluster for Gc is observed in the temporal BA 38, whereas non-overlapping clusters for Gv are located in BA 44 (frontal lobe) and BA 17 (occipital lobe).

intelligence volumetric correlates are largely distributed, and (c) measures of crystallized intelligence correlate with volumes primarily within the temporal lobes.

### 3. Discussion

#### 3.1. Relationship to P-FIT

The results reported here with respect to general intelligence are highly consistent with the parieto-frontal integration theory of intelligence (P-FIT) (Jung & Haier, 2007). Virtually all identified clusters of voxels correlating with the general intelligence score are located in brain areas underscored by the theoretical model (Figs. 1 and 6).

Nevertheless, there are small differences: clusters of voxels located in frontal Brodmann areas (BAs) 8 (frontal eye fields –involved in planning complex movements) and BA 11 (orbitofrontal area –implicated in reasoning, planning, and decision making), as well as in temporal BAs 20–21 (inferior and middle temporal gyrus, dedicated to high-level visual processing, recognition memory, auditory processing, and language), BA 36 (parahippocampal cortex, closely related to the fusiform gyrus), and BA 42 (auditory association cortex) were not included within the proposed theoretical model, but were identified in the present study.

Findings for the pure estimates of crystallized and spatial intelligence have not been reported before and warrant some comment. It is important to highlight that these estimates were uncorrelated with general (fluid) intelligence. Table 2 showed that general intelligence was related to all the measures in the battery, whereas the pure estimates for crystallized and spatial intelligence were related to their respective measures only. Therefore, findings for these latter estimates speak about verbal (Gc) and spatial (Gv) intelligence controlling for the pervasive influence of g.

We found overlapping clusters located in several brain areas for these two pure estimates of verbal and spatial intelligence, irrespective of the fact that their correlation is zero (Fig. 6): (a) frontal BAs 8 (frontal eye fields) and 11 (orbitofrontal area); (b)

parietal BAs 5 and 7 (somato-sensory association cortex), and 40 (supramarginal gyrus part of Wernicke's area); (c) temporal BAs 20 (inferior temporal gyrus) and 39 (angular gyrus part of Wernicke's area), and (d) occipital BAs 18 and 19 (visual cortex). As noted above, most of these areas overlap with general intelligence, regardless of the fact that their correlation is also zero. This suggests that there might be common brain areas underlying individual differences in unrelated facets of the intelligence construct (see below).

#### 3.2. The neuroanatomy of intelligence

The areas we find here related to intelligence have a number of theoretically relevant cognitive functions.

Frontal BAs 9–10 and 46 comprise the dorsolateral prefrontal cortex. This brain region is thought to play a role in sustaining attention and in working memory (Kane & Engle, 2002; Ramnani & Owen, 2004; Wager & Smith, 2003). Together with BA 11, it is involved in planning, reasoning, decision making, memory retrieval, and executive functioning. BA 45 includes Broca's area, and is implicated in semantic decision tasks, verb generation, and semantic working memory processes. It guides recovery of semantic information and evaluates this information within a given context. BA 47 is implicated in the processing of syntax. The role of BAs 5 (somato-sensory association cortex), 6 (pre-motor and supplementary motor cortex), and 8 (frontal eye fields) are less clear for intelligence. This latter area is involved in planning complex movements, so perhaps it can be considered that this region works in tandem with other frontal areas towards evaluation and hypothesis testing components. Further, assuming higher intelligence led to greater survival, these somato-sensory areas might have evolved together with "thinking" areas because they were important for running away effectively, articulating coping strategies, and so forth.

Parietal BA 7 (somato-sensory association cortex) is implicated in locating objects in space. Vision and proprioception converge on this brain area. BA 40 (supramarginal gyrus part of Wernicke's area) receives input from multiple sensory



Shaw's (2007) recent summary of the research regarding neuroimaging of intelligence is consistent with the generalist genes hypothesis, the P-FIT model, and the main results reported in the present article: "the weight of evidence suggests intelligence is a distributed property of multiple interconnected cortical regions (...) the unitary theoretical construct of g may represent the emergent property of concerted action of a host of physiological and psychological processes" (p. 964).

The dynamic model of general intelligence proposed by Van der Maas et al. (2007) based on a mathematically formulated developmental model relying on the so-called mutualism (i.e. positive beneficial relationships between cognitive processes) should also be considered within this framework. This model is thought to identify a plausible mechanism giving rise to the positive manifold behind g, but without including g as a latent factor. Van der Maas et al. (2007) suggest that psychometric g need not correspond to an actual quantitative variable, such as brain size. A similar model has been proposed by Dickens (2007) to account for the Flynn effect.

This is the important message: it is possible to empirically identify discrete brain areas wherein volumetric variations are related to the intelligence construct (Colom et al., 2006a,b, 2007; Frangou, Chitins, & Williams, 2004; Gong et al., 2005; Haier et al., 2004, 2005; Johnson et al., 2008; Wilke, Sohn, Byars, & Holland, 2003). Moreover, variations in the volume of these brain regions are clearly related to individual differences in intelligence in normal populations. Volumes of these brain structures are determined by the number and size of neurons. Therefore, greater volumes could implicate more efficient working structures.

The parieto-frontal integration theory (P-FIT) of intelligence is generally supported by the findings reported in the present article, and both are consistent with the generalist genes hypothesis. Results shown for the refined estimates of general (g), crystallized, and spatial intelligence are consistent with the view that cognitive abilities are supported by both common and unique discrete brain regions.



# The neuroscience of human intelligence differences

*Ian J. Deary, Lars Penke and Wendy Johnson*

**Abstract** | Neuroscience is contributing to an understanding of the biological bases of human intelligence differences. This work is principally being conducted along two empirical fronts: genetics — quantitative and molecular — and brain imaging. Quantitative genetic studies have established that there are additive genetic contributions to different aspects of cognitive ability — especially general intelligence — and how they change through the lifespan. Molecular genetic studies have yet to identify reliably reproducible contributions from individual genes. Structural and functional brain-imaging studies have identified differences in brain pathways, especially parieto-frontal pathways, that contribute to intelligence differences. There is also evidence that brain efficiency correlates positively with intelligence.



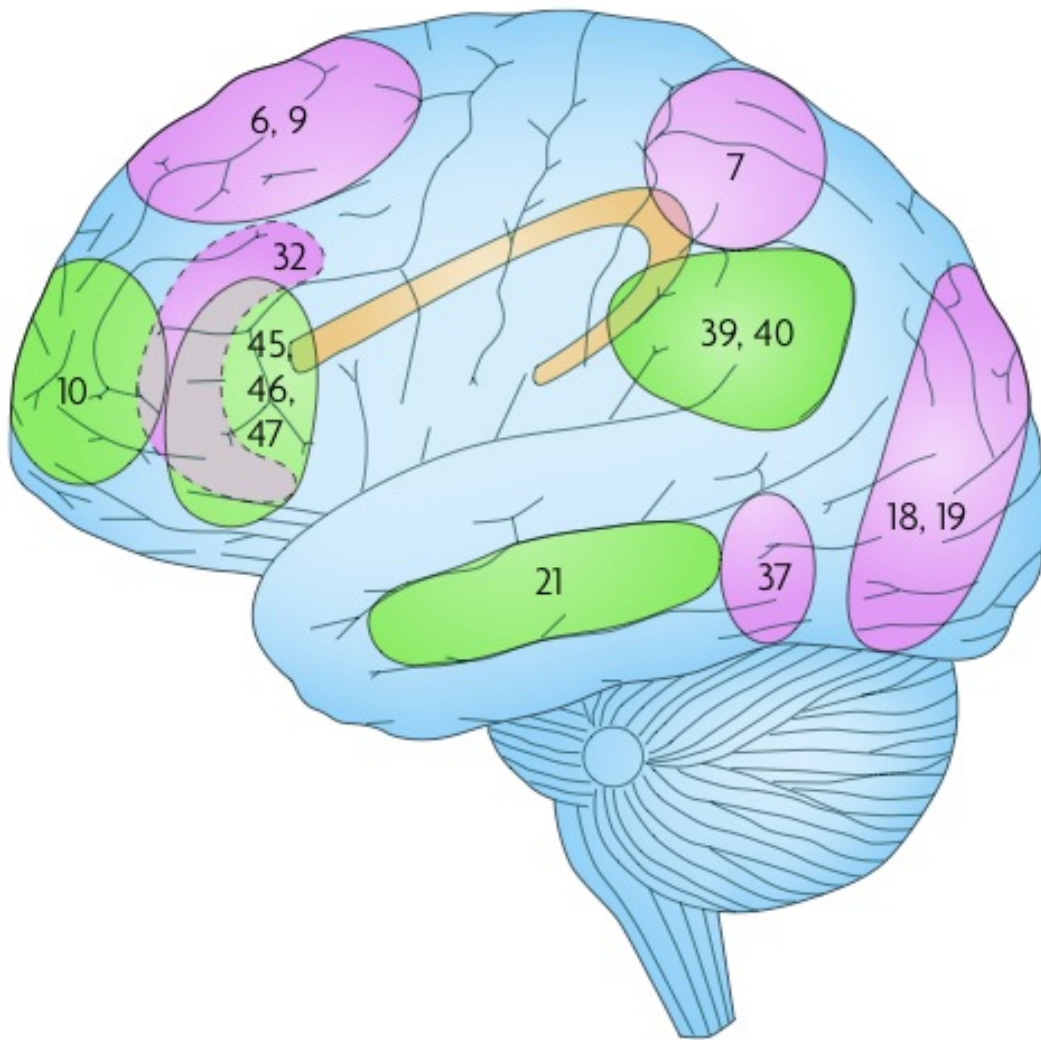


Figure 2 | **The loci of intelligence differences.** Based on a review of all the structural and functional neuroimaging literature that was available, Jung and Haier proposed the parieto-frontal integration theory of intelligence (P-FIT), which is arguably the best available description of how intelligence is distributed in the brain. The figure shows Brodmann Areas (BAs) involved in intelligence, as well as the arcuate fasciculus (shown in yellow) as a promising candidate for a white matter tract that connects the involved brain regions. BAs shown in green indicate predominantly left-hemispheric correlations and BAs shown in pink indicate predominantly right-hemispheric correlations with intelligence. Figure is modified, with permission, from REF. 60 © (2007) Cambridge University Press.



grey matter (that is, mostly nerve cell bodies, but also dendrites and supportive glia cells) from those of white matter (that is, nerve cell axons). This approach usually yields slightly higher correlations between intelligence and overall grey matter ( $r \sim 0.31$ ) than between intelligence and overall white matter ( $r \sim 0.27$ ), although differences are usually small<sup>19</sup>.

Several studies have used voxel-based morphometry on MRI scans to measure the volume of grey matter (and less frequently white matter) in specific brain regions, and to relate this to measures of intelligence. Most of this work has been summarized by Jung and Haier<sup>60</sup>, who assigned the existing results to Brodmann areas (BAs) and concluded that a network of brain regions — including areas in the dorsolateral prefrontal cortex, parietal lobe, anterior cingulate cortex and specific regions in the temporal and occipital lobe — relate to individual differences in intelligence (FIG. 2).

According to this parieto-frontal integration theory of intelligence (P-FIT), the extrastriate cortex (BAs 18–19) and fusiform gyrus (BA 37) are involved in intelligence test performance because they contribute to the recognition, imagery and elaboration of visual input, just as Wernicke's area (BA 22) does for syntactic auditory input. Information captured through these pathways is then processed in the supramarginal (BA 40), superior parietal (BA 7), and angular (BA 39) gyri of the parietal lobe, in which structural symbolism, abstraction and elaboration are thought to emerge. These parietal regions may then interact with parts of the frontal lobe (especially BAs 6, 9, 10, 45, 46 and 47) to form a working memory network that compares different possible task responses. Once a task response is selected, the anterior cingulate cortex (BA 32) supports response engagement and inhibition of alternative responses. These interactions among brain regions are dependent on the white matter fibres that connect them, such as the arcuate fasciculus. For most of these brain regions, the left hemisphere seems to be more important to cognitive task performance than the right hemisphere. As subsequent studies<sup>61,62</sup>, and also studies using different methodologies (see below), have generally confirmed this theory (but see also REF. 63), P-FIT can be considered the best available answer to the question of where in the brain intelligence resides.

Cortical thickness, which more accurately reflects the cytoarchitectural characteristics of the neuropil than measures of grey matter volume<sup>64</sup>, has been related to intelligence in four studies so far<sup>29,38,64,65</sup>. They all found generally (though not exclusively<sup>29,65</sup>) positive correlations between intelligence and cortical thickness, especially in the prefrontal cortex<sup>29,38,64</sup> and temporal lobes<sup>29,38,65</sup>, as well as clustered around areas of multimodal association<sup>64</sup>.

All of these studies on (sometimes extremely fine-grained) measures of brain size and intelligence are correlational; the exact relation between the quantity of brain tissue and the quality of cognitive functions is largely unknown<sup>66,67</sup>. Although larger brains, greater grey matter volumes and thicker cortices usually are associated with more neurons, it is unclear how and why this should lead to better intellectual performance, especially

as brain development — and presumably intelligence development — involves substantial neuronal pruning<sup>68</sup>. This issue is also relevant in macrocephaly, in which pathologically enlarged brains are associated with decreased rather than increased cognitive function.

Related questions were raised in a longitudinal study by Shaw and colleagues<sup>17</sup>. They showed that the trajectories of development of cortical thickness in children differed for groups of different intelligence. Children with the highest intelligence scores had comparatively thin cortices in early childhood, but showed more rapid increases in thickness in the prefrontal and temporal lobes until puberty, when all cortices slowly thinned. Thus, it is possible that differences in brain development have an underappreciated role in intelligence differences.

A different, more direct way to test whether a brain area is crucially involved in intelligence differences is provided by studies of people with brain lesions. Lesion studies have a long history in the neuroscience of intelligence. However, it was only recently that the limited applicability and specificity of case or small-sample studies of focal brain damage were overcome by Gläscher and colleagues, who collected cognitive data from a large sample of 241 patients with brain lesions<sup>69</sup>. Using voxel-based lesion mapping, they found highly specific lesion–deficit relations in left frontal and parietal cortex for working memory efficiency, in the left inferior frontal cortex for verbal comprehension and in right parietal cortex for perceptual organization — all subfactors of general intelligence.

**The (dis)connected mind.** There is an emerging consensus that intelligence does not reside in a single, narrowly circumscribed brain region such as the frontal lobe. Rather, intelligence seems to be best described as a small-world network<sup>70–72</sup>. This model implies that high intelligence probably requires uninterrupted information transfer among the involved brain regions along white matter fibres.

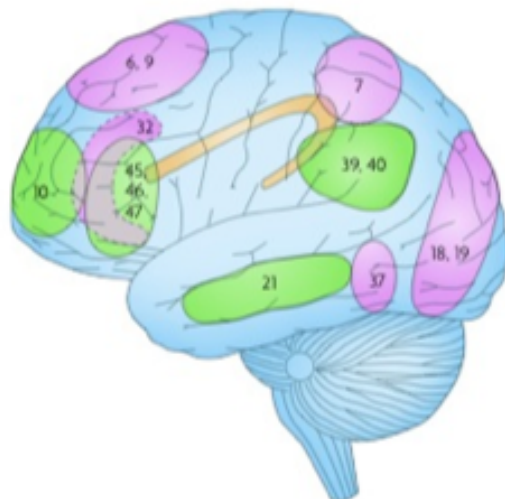
One way to study white matter in relation to intelligence is to quantify white matter lesions on MRI or computed tomography scans. Because white matter is especially prone to age-related decline, these lesions have been studied mainly in elderly subjects. These studies found weak but consistent relationships indicating that people with more white matter lesions have lower cognitive ability<sup>74,75</sup>. The small effect sizes reported in this literature are probably partly due to the fact that most studies rely on lesion rating scales that allow for a considerable degree of subjectivity. Improving these by using multiple raters increased the association<sup>76</sup>.

So far, 11 studies across a range of age groups have applied <sup>1</sup>H-magnetic resonance spectroscopy to examine white matter integrity in relation to intelligence<sup>77</sup>. Although methods and results were heterogeneous, the studies generally found positive correlations between intelligence and concentrations of N-acetyl aspartate, a metabolite of the oligodendrocytes that form the myelin sheath around nerve fibres, and various white and grey matter areas in the brain, supporting the proposed role of white matter in intelligence.

#### Small-world network

A network characterized by high levels of local clustering among nodes and short paths that globally link all nodes, resulting in all nodes being linked through few intermediate steps despite few connections per node.





**Figure 2 | The loci of intelligence differences.** Based on a review of all the structural and functional neuroimaging literature that was available, Jung and Haier proposed the parieto-frontal integration theory of intelligence (P-FIT), which is arguably the best available description of how intelligence is distributed in the brain. The figure shows Brodmann Areas (BAs) involved in intelligence, as well as the arcuate fasciculus (shown in yellow) as a promising candidate for a white matter tract that connects the involved brain regions. BAs shown in green indicate predominantly left-hemispheric correlations and BAs shown in pink indicate predominantly right-hemispheric correlations with intelligence. Figure is modified, with permission, from REF. 60 © (2007) Cambridge University Press.

Studies using diffusion tensor (DT)-MRI showed significant correlations between water diffusion parameters that quantify white matter integrity and intelligence in children<sup>76,79</sup>, young adults<sup>80</sup> and old adults<sup>78,81</sup>, especially in the centrum semiovale. Consistent with these findings, two studies that applied tractography on DT-MRI data to calculate integrity indices for specific white matter tracts found positive correlations between cognitive ability and white matter integrity, especially for long association fibres, such as the arcuate and uncinate fasciculi<sup>75,82</sup>. One study using cognitive data spanning several decades found a significant association between childhood IQ and white matter integrity in old age<sup>78</sup>. This suggests that, in addition to the probably direct contribution of white matter integrity to intelligence, higher intelligence might result in behaviours across the life-course that promote white matter integrity. Alternatively, it is possible that intelligence and white matter integrity have, from an early age, overlapping sets of genetic and/or environmental inputs.

In a resourceful use of the 79 healthy adults from REF. 82, Li and colleagues combined DT-MRI tractography and MRI with graph analysis to construct a global brain network<sup>71</sup>. They found significant correlations between intelligence and parameters that reflect white matter network efficiency, indicating that not only the integrity, but also the organizational efficiency, of white matter is important for higher intelligence.

**Efficient processing.** Early functional studies of intelligence used behavioural measures of reaction and inspection time<sup>12</sup> and correlated them with various measures of cognitive ability. The well-established finding is that more intelligent people react to and inspect visual and auditory stimuli **more rapidly** than less intelligent people. However, although such chronometric tasks are generally thought to be endophenotypes of intelligence, it has yet to be established whether they are more biologically tractable than is intelligence itself.

More recently, electroencephalography (EEG), positron emission tomography (PET), regional cerebral blood flow (rCBF) analysis and functional MRI (fMRI) have been used extensively on individuals performing intelligence-related tasks such as matrix reasoning, mental rotation or playing the video game Tetris. The indices of brain functional activity provided by these methods were interpreted as measures of neuronal efficiency and related to performance on the current task and/or on intelligence tests taken before or afterwards. This literature has recently been reviewed in detail<sup>60,83</sup>, and two basic conclusions were drawn: first, similar to structural studies, functional studies support a distributed network perspective on intelligence, largely overlapping with the one shown in FIG. 2 and discussed above<sup>60</sup>. Second, functional neuroimaging findings are generally consistent with the hypothesis that intelligent brains process information more efficiently (that is, use fewer brain resources when performing cognitive tasks) than less intelligent brains<sup>84</sup>, provided that the cognitive task is difficult enough to discriminate between intelligent and less intelligent individuals, but not so difficult that even the most intelligent individuals have to recruit all their brain resources to solve it. In the case of these more difficult tests, less intelligent individuals usually give up, resulting in a positive correlation between brain resource usage and intelligence<sup>85</sup>.

The notion that brain efficiency has a role in intelligence is also supported by a study by van den Heuvel and colleagues<sup>86</sup>. Similar to the approach of Li *et al.* for white matter networks<sup>71</sup>, they used graph analysis to assess the efficiency of a global brain network constructed using a voxel-wise approach based on fMRI data obtained at rest. They found significant links between functional efficiency and IQ, especially in frontal and parietal regions. This is consistent with another fMRI study which reported significant correlations between IQ and the resting-state functional connectivity of an 'exploratory' network involving the frontal and the parietal, occipital and limbic lobes<sup>86</sup>. The brain areas that were activated as an efficient network during resting periods (with less activity in more intelligent individuals) in these two studies matched the frontal and parietal regions that were found to be activated in intelligent subjects under high cognitive demand<sup>60,83</sup>. This indicates that brain activity can be used to distinguish more and less intelligent people even when they are not cognitively challenged.

**Many neuronal roads to intelligence.** Many studies on the neuroscience of intelligence have shown sex differences, sometimes to a striking degree,



#### Long association fibre

A member of a set of axonal tracks connecting distant brain areas in the same hemisphere.

#### Network efficiency

Describes short mean path lengths for parallel information transfer — as provided by a small-world network structure, for example.

#### Functional connectivity

Correlations between the activation patterns of different brain areas.

Performance on all of the cognitive tasks and abilities studied in neuroscience and genetics are confounded by general intelligence. Therefore, if researchers are primarily interested in the brain areas or genes for a specific cognitive ability, it might be helpful to statistically control for g, which should isolate as well as possible what is unique to a single task (see REF. 97).

The brains of some people are more efficient than those of others. The biological foundations of these differences are of great interest to basic and applied neuroscience. There are already some well-replicated general findings. The differential neuroscience of human intelligence therefore has a strong mandate and a firm foundation from which to proceed.



## ORIGINAL ARTICLE

# Brain white matter tract integrity as a neural foundation for general intelligence

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General intelligence is a robust predictor of important life outcomes, including educational and occupational attainment, successfully managing everyday life situations, good health and longevity. Some neuronal correlates of intelligence have been discovered, mainly indicating that larger cortices in widespread parieto-frontal brain networks and efficient neuronal information processing support higher intelligence. However, there is a lack of established associations between general intelligence and any basic structural brain parameters that have a clear functional meaning. Here, we provide evidence that lower brain-wide white matter tract integrity exerts a substantial negative effect on general intelligence through reduced information-processing speed. Structural brain magnetic resonance imaging scans were acquired from 420 older adults in their early 70s. Using quantitative tractography, we measured fractional anisotropy and two white matter integrity biomarkers that are novel to the study of intelligence: longitudinal relaxation time (T1) and magnetisation transfer ratio. Substantial correlations among 12 major white matter tracts studied allowed the extraction of three general factors of biomarker-specific brain-wide white matter tract integrity. Each was independently associated with general intelligence, together explaining 10% of the variance, and their effect was completely mediated by information-processing speed. Unlike most previously established neurostructural correlates of intelligence, these findings suggest a functionally plausible model of intelligence, where structurally intact axonal fibres across the brain provide the neuroanatomical infrastructure for fast information processing within widespread brain networks, supporting general intelligence.

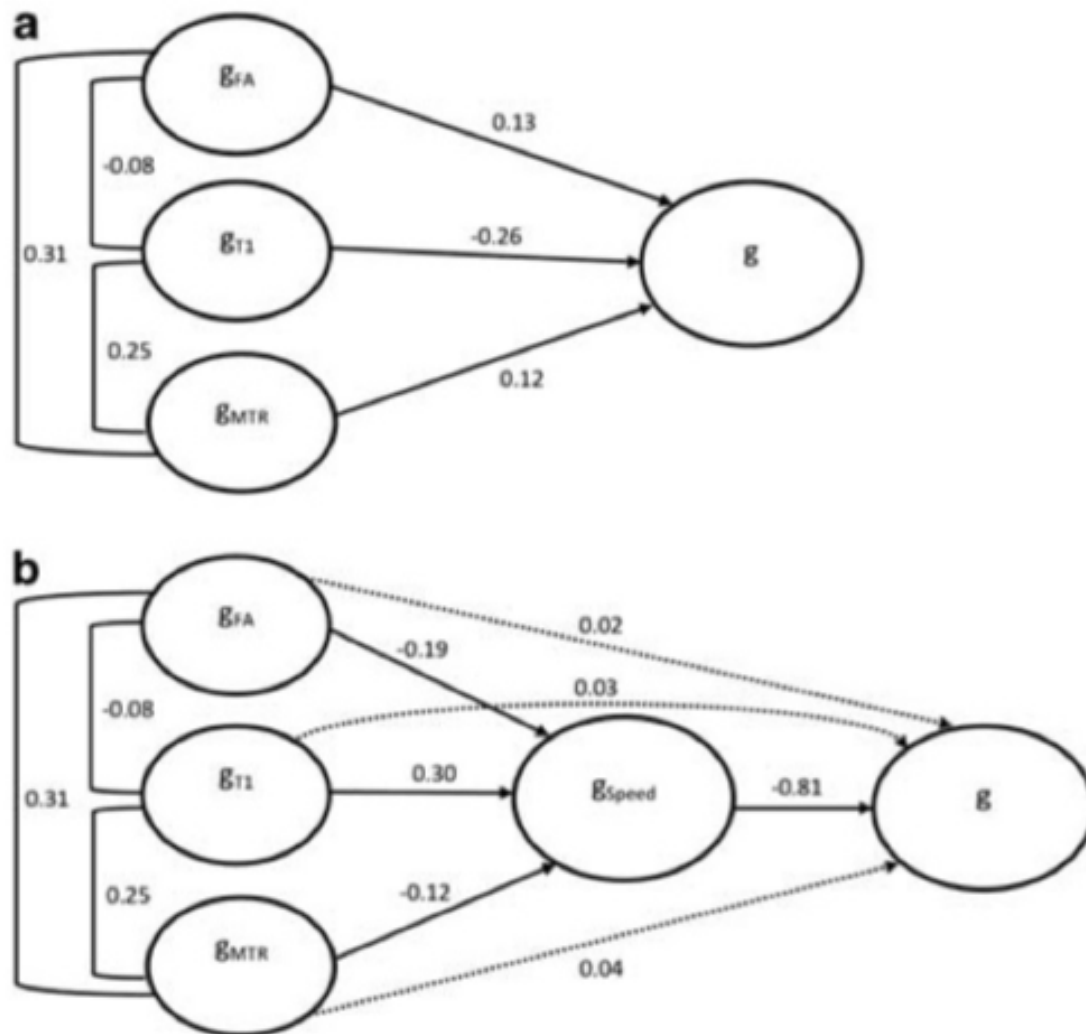
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**Keywords:** diffusion tensor imaging; information-processing speed; intelligence; magnetisation transfer imaging; tractography; white matter

Combined, the three biomarkers of brain-wide white matter tract integrity explained 10% of the intelligence differences in our older sample and even more of the differences in information-processing speed. The large sample size implies that the effect estimates are likely to be robust. These effect sizes do compare with that of the best-replicated neuroanatomical correlate of intelligence, brain size.<sup>2,41</sup> However, the present study's results are based on a more tractable set of brain biomarkers; it is far from clear why brain size affects cognitive performance.<sup>2,42</sup> By contrast, white matter tracts constitute the neuroanatomical infrastructure for any brain network model of cognitive performance,<sup>14</sup> and tract integrity can be directly linked to cognitive information-processing speed and via this mediating path to general intelligence. Although there might be several heterogeneous neurostructural substrates underlying intelligence,<sup>43,44</sup> the current study provides empirical evidence for one mechanistically plausible neurostructural model of human intelligence differences.







**Figure 2.** Results of SEM of the three white matter integrity factors, general intelligence, and information-processing speed. Only the latent variables are depicted. For full measurement models see Supporting Online Materials. All path estimates are standardised. **(a)**  $g_{FA}$ ,  $g_{T1}$  and  $g_{MTR}$  (common latent factors each defined by their respective tractography estimate for all 12 tracts) are independently associated with general intelligence ( $g$ ) ( $\chi^2(755) = 1721.27$ , CFI = 0.945, NNFI = 0.938, RMSEA = 0.055, SRMR = 0.054), explaining 10.0% of the variance. **(b)** Cognitive information-processing speed ( $g_{Speed}$ ) mediates the association between the three latent white matter tract integrity factors and general intelligence. Note that higher values of  $g_{Speed}$  indicate slower (less favourable) information-processing speed. The model with solid lines fits the data well ( $\chi^2(880) = 1900.894$ , CFI = 0.943, NNFI = 0.936, RMSEA = 0.053, SRMR = 0.053, AIC = 36524.9, BIC = 37151.1). Additional direct paths from  $g_{FA}$ ,  $g_{T1}$  and  $g_{MTR}$  to  $g$  (dotted lines) have negligible, non-significant path estimates and decrease model fit (AIC = 36530.1, BIC = 37168.5), indicating full mediation of the effect of the three white matter tract integrity indices on general intelligence by cognitive information-processing speed.



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## Feature Review

# Large-scale brain networks in cognition: emerging methods and principles

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**An understanding of how the human brain produces cognition ultimately depends on knowledge of large-scale brain organization. Although it has long been assumed that cognitive functions are attributable to the isolated operations of single brain areas, we demonstrate that the weight of evidence has now shifted in support of the view that cognition results from the dynamic interactions of distributed brain areas operating in large-scale networks. We review current research on structural and functional brain organization, and argue that the emerging science of large-scale brain networks provides a coherent framework for understanding of cognition. Critically, this framework allows a principled exploration of how cognitive functions emerge from, and are constrained by, core structural and functional networks of the brain.**

cognition by revealing how cognitive functions arise from interactions within and between distributed brain systems. It focuses on technological and methodological advances in the study of structural and functional brain connectivity that are inspiring new conceptualizations of large-scale brain networks. Underlying this focus is the view that structure–function relations are critical for gaining a deeper insight into the neural basis of cognition. We thus emphasize the structural and functional architectures of large-scale brain networks (Box 1). For this purpose, we

## Glossary

**Blood-oxygen-level-dependent (BOLD) signal:** measure of metabolic activity in the brain based on the difference between oxyhemoglobin and deoxyhemoglobin levels arising from changes in local blood flow.

**Central-executive network (CEN):** brain network responsible for high-level cognitive functions, notably the control of attention and working memory.





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**Central-executive network (CEN):** brain network responsible for high-level cognitive functions, notably the control of attention and working memory.

**Default-mode network (DMN):** large-scale network of brain areas that form an integrated system for self-related cognitive activity, including autobiographical, self-monitoring and social functions.

**Diffusion-based tractography:** class of noninvasive magnetic resonance imaging techniques that trace fiber bundles (white matter tracts) in the human brain *in vivo* based on properties of water molecule diffusion in the local tissue microstructure.

**Dynamic causal modeling:** statistical analysis technique based on bilinear dynamic models for making inferences about the effects of experimental manipulations on inter-regional interactions in latent neuronal signals.

**Functional interdependence:** statistical inter-relation of variables representing temporal changes in different network nodes.

**Granger causality analysis (GCA):** statistical method that, when applied to the brain, measures the degree of predictability of temporal changes in one brain area that can be attributed to those in another area.

**Independent component analysis (ICA):** computational technique that separates a multivariate signal into additive components based on the assumption that the components arise from statistically independent non-Gaussian sources.

**Intrinsic connectivity network (ICN):** large-scale network of interdependent brain areas observed at rest.

**Large-scale:** term referring to neural systems that are distributed across the entire extent of the brain.

**Local field potential (LFP):** electric potential generated in a volume of neural tissue by a local population of neurons. LFPs result from the flow of current in the extracellular space generated by electromotive forces operating across the cell membranes of neurons, principally at synapses.

**Functional magnetic resonance imaging (fMRI):** noninvasive neuroimaging method that measures BOLD signals in the brain *in vivo*.

**Network:** physical system that can be represented by a graph consisting of nodes and edges.

**Network edge:** component of networks that links nodes.

**Network node:** component of networks linked by edges.

**Phase synchrony:** tendency for two time series to exhibit temporal locking, or a constant relative phase relation, usually in a narrow frequency range.





**Box 1. The concept of brain networks**

Brain networks can be defined based on structural connectivity or functional interdependence. The structural network organization of the brain is based on the anatomical linkage of its neurons. Neurons are connected locally by synapses from short axons, dendrites and gap junctions. Although neuronal populations throughout the brain have a variety of different internal circuitry configurations, they can be represented as network nodes if they have a uniquely identifiable local structural organization, a large-scale structural connectivity pattern or a local functional activity pattern that allows them to be distinguished from their neighbors.

Some (projection) neurons in the brain have long axons that synapse at a distance from the cell body. Long axon pathways that project from one neuronal population to another can be represented as network edges. If the pathway between two populations (A and B) consists of axons only from A to B or only from B to A, then the edge can be considered to be directed. If the pathway consists of axons in both directions, then the edge can be considered to be bidirectional. If the method used to identify edges in the brain does not establish directionality, the edges can be treated as being undirected.

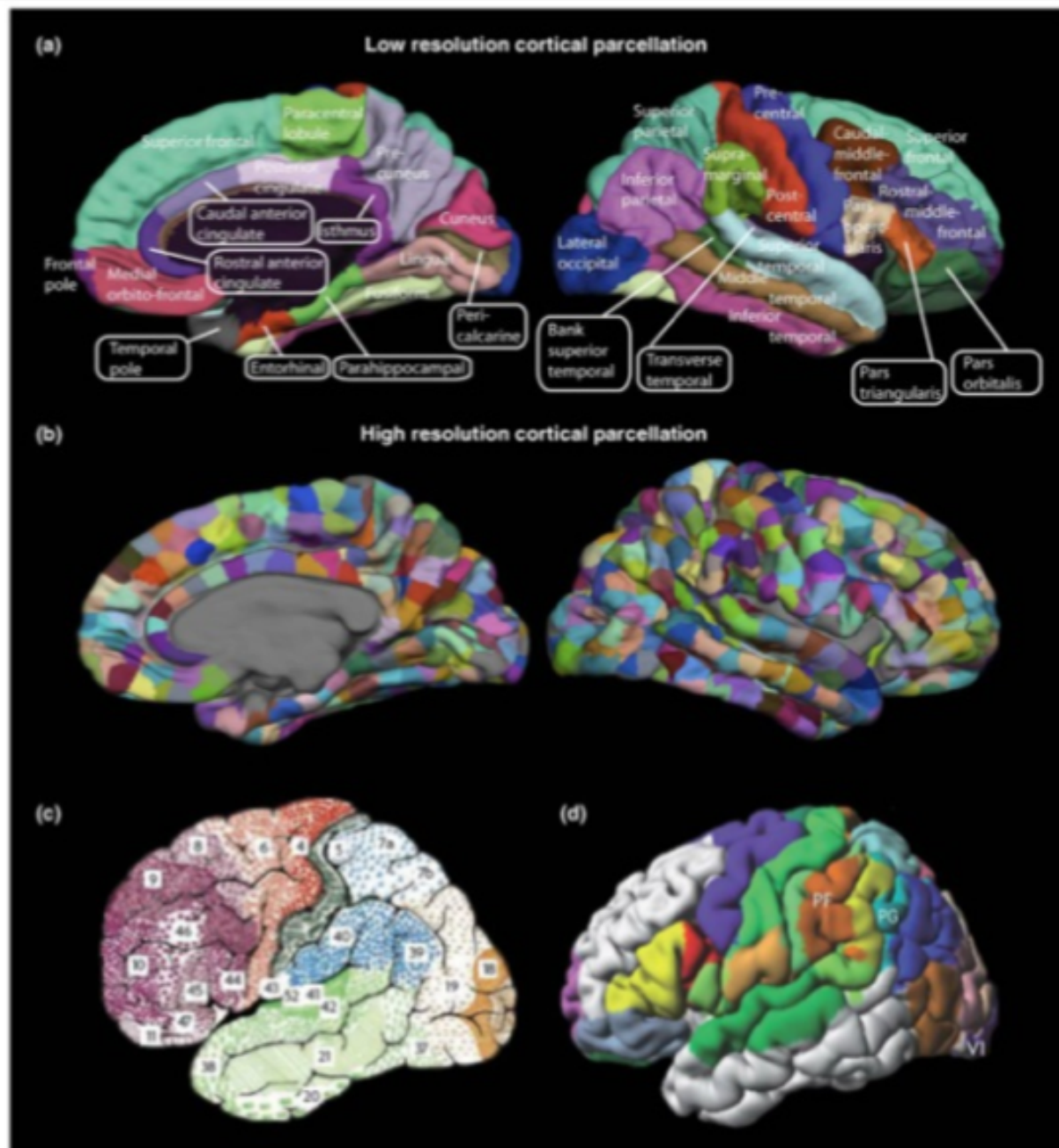
The functional interdependence of brain network nodes refers to joint activity in different brain structures that is co-dependent under variation of a functional or behavioral parameter. Most methods yield non-zero values of functional interdependence in all cases, so true functional interdependence must depend on values that are significantly different from zero or significantly different between cognitive conditions.

framework allows a more systematic examination of how cognitive functions emerge from, and are constrained by, core structural and functional networks of the brain. Finally, we suggest some directions in which we expect research in this field to proceed in the future.

**Large-scale structural brain networks**

The neuroanatomical structure of large-scale brain networks provides a skeleton of connected brain areas that facilitates signaling along preferred pathways in the service of specific cognitive functions. It is important to identify the brain areas that constitute structural network nodes and the connecting pathways that serve as structural network edges to know which configurations of interacting areas are possible. In the past, large-scale structural brain networks were often schematized by two-dimensional wiring diagrams, with brain areas connected by lines or arrows representing pathways. Currently, more sophisticated network visualization and analysis schemes are being developed and used [19]. We focus here first on the principal methods used to define structural nodes and edges in the brain. We then consider some possible functional consequences of the structural organization of large-scale brain networks.





**Figure 1.** Identification of large-scale structural network nodes in the human brain by four methods currently in use. **(a)** Automated parcellation of a single subject's structural MR image into nodes based on the geometry of large sulcal landmarks. **(b)** High-resolution parcellation with arbitrary granularity. (Reproduced with permission from [35].) **(c)** Classical Brodmann atlas based on cytoarchitectonic features. **(d)** The Jülich-Düsseldorf cytoarchitectonic probabilistic brain atlas, based on observer-independent mapping of cortical areas in ten post-mortem brains. (Not all brain areas are currently covered in this scheme.) (Reproduced with permission from [160].)





## Large-scale functional brain networks

The primate brain has evolved to provide survival value to primate species by allowing individual species members to behave in ways that accommodate a wide variety of environmental contingencies, performing different behaviors under different sets of conditions. At each moment, a specific set of conditions must be analyzed by the perceptual apparatus of the brain and sets of percepts must be combined with learned concepts to create a 'solution' to the immediate problem of understanding the environment and acting appropriately. It is reasonable to assume that collections of interconnected brain areas act in concert to produce these solutions, as well as corresponding behaviors, and that they interact dynamically to achieve concerted action [49]. A large-scale functional network can therefore be defined as a collection of interconnected brain areas that interact to perform circumscribed functions.

Structural networks provide a complex architecture that promotes the dynamic interactions between nodes that give rise to functional networks. The connectivity patterns of structural networks, which vary with species [50], determine the functional networks that can emerge. Some functional networks, such as for language, depend on species-specific structural specializations [51], whereas others are common across species. The topological form of functional networks (which nodes are connected to which other nodes) changes throughout an individual's lifespan and is uniquely shaped by maturational and learning processes within the large-scale neuroanatomical connectivity matrix for each individual [52].

Large-scale functional networks in the brain exert coordinated effects on effector organs, subcortical brain structures and distributed cortical areas during a host of different cognitive functions. Component brain areas of large-scale functional networks perform different roles, some acting as controllers that direct the engagement of other areas [53] and others contributing specific sensory or conceptual content to network operations. For instance, coordinated prefrontal and posterior parietal control areas channel the flow of activity among sensory and motor areas in preparation for, and during, perceptuomotor processing [54–57].

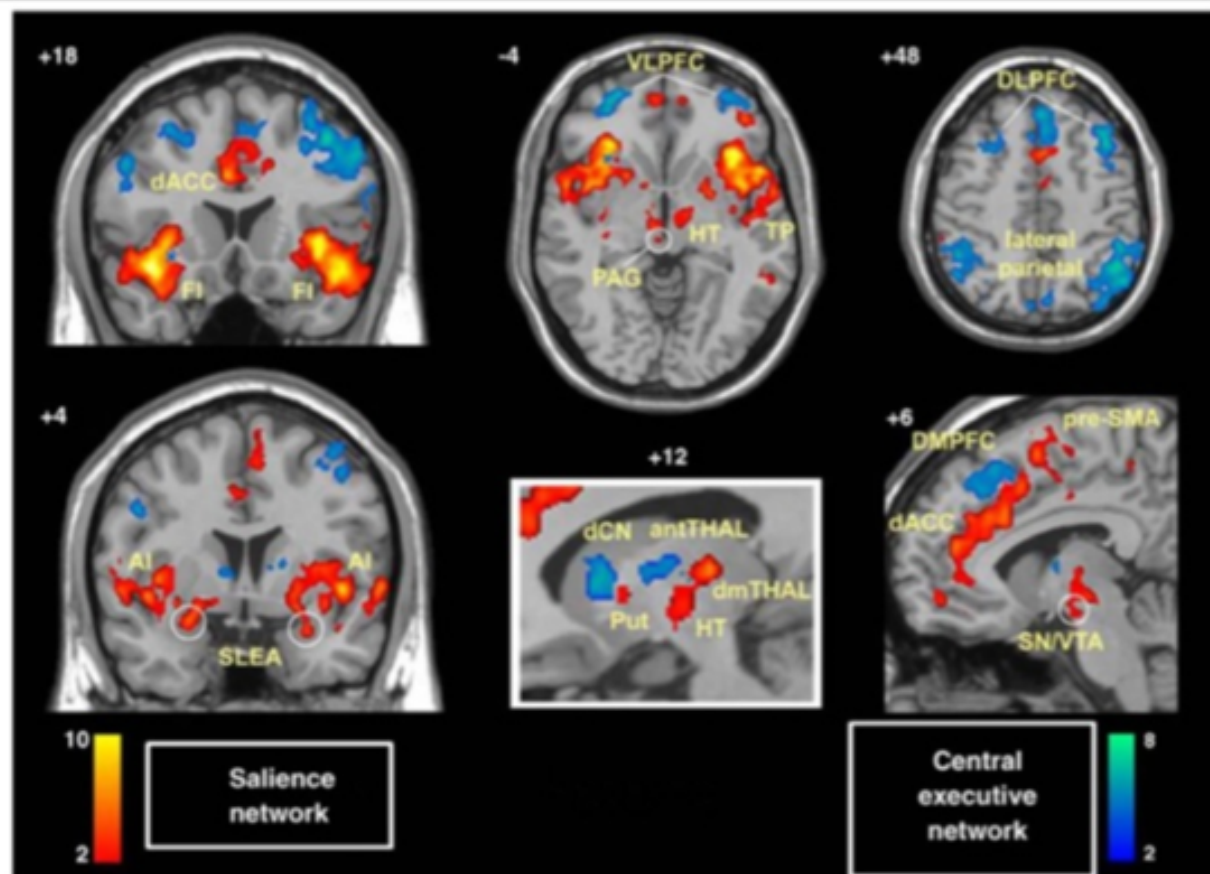


lower-order visual network [105,107]. This technique has allowed intrinsic (Figure 5), as well as task-related (Figure 6), fMRI activation patterns to be used for identification of distinct functionally coupled systems, including a central-executive network (CEN) anchored in dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC), and a salience network anchored in anterior insula (AI) and anterior cingulate cortex (ACC) [107].

A second major method of CEN identification is seed-

## Review

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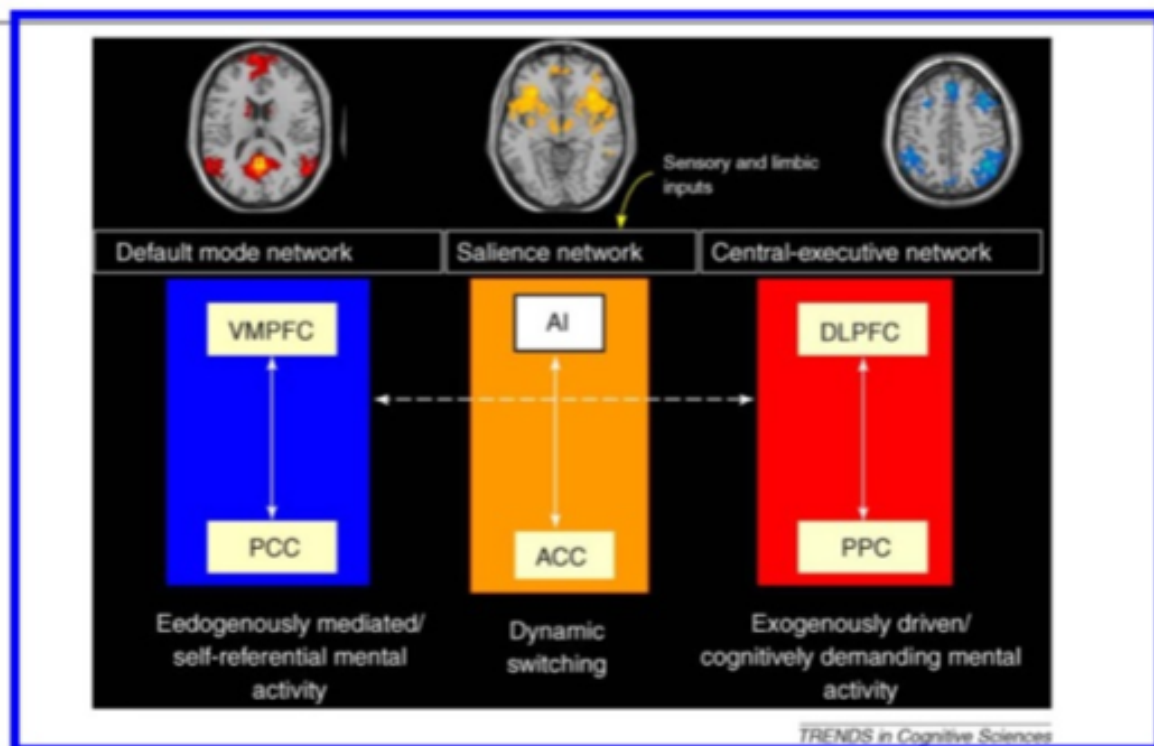


**Figure 5.** Two core brain networks identified using intrinsic physiological coupling in resting-state fMRI data. The salience network (shown in red) is important for monitoring the salience of external inputs and internal brain events, and the central-executive network (shown in blue) is engaged in higher-order cognitive and attentional control. The salience network is anchored in anterior insular (AI) and dorsal anterior cingulate cortices (dACC), and features extensive connectivity with subcortical and limbic structures involved in reward and motivation. The central-executive network links the dorsolateral prefrontal and posterior parietal cortices, and has subcortical coupling that is distinct from that of the salience network. (Reproduced with permission from [107].)



medial PFC in social cognitive processes related to self and others [122], the MTL in episodic memory [123], and the angular gyrus in semantic processing [124]. These studies suggest that the functions of the DMN nodes are very different. However, when considered as a core brain network, the DMN is seen to collectively comprise an integrated system for autobiographical, self-monitoring and social cognitive functions [125], even though a unique

ways in which it interacts with other networks. we use the **salience network** to illustrate this point. As described above, it has been suggested that this network **mediates attention to the external and internal worlds** [130]. To determine whether this network indeed specifically performs this function will require testing and validation of a sequence of putative network mechanisms that includes: (i) bottom-up detection of salient events; (ii) switching



**Figure 7.** **Multi-network switching** initiated by the salience network. It is hypothesized that the salience network initiates **dynamic switching** between the central-executive and default-mode networks, and mediates between attention to endogenous and exogenous events. In this model, sensory and limbic inputs are processed by the AI, which detects salient events and initiates appropriate control signals to regulate behavior via the ACC and homeostatic state via the mid and posterior insular cortex. Key nodes of the salience network include the AI and ACC; the default-mode network includes the VMPFC and PCC; the central-executive network includes the DLPFC and PPC. (Based on [129] and [130].)





### Functional brain networks and psychopathology

The systematic exploration of large-scale functional brain networks is yielding not only parsimonious accounts of normal cognitive processes, but also novel insights into psychiatric and neurological disorders [131–133]. Abnormalities in intrinsic functional connectivity have been identified within the DMN in Alzheimer's disease [134,135] and in major depression [131], albeit in different network nodes. Abnormalities have been observed in the phase synchrony of oscillatory neuronal population activity [136] in relation to Alzheimer's disease [137], schizophrenia [138–140], autism [141–143], the manic phase of bipolar disorder [144] and Parkinson's disease [145]. Thus, impairment of functional network interactions might be common in psychiatric and neurological disorders, and observable by functional interdependence analysis of both oscillatory neuronal population and fMRI activity.

A particularly striking example of this new view of psychopathology comes from the finding, discussed above, that the AI is a critical node for initiation of network switching. This key insight reveals the potential for profound deficits in cognitive functioning should AI integrity or connectivity be compromised. AI hyperactivity has been implicated in anxiety disorders, suggesting that salience network hyperactivity can be pathological [146]. Individuals scoring high on the trait neuroticism, the tendency to experience negative emotional states, demonstrate greater AI activation during decision-making even when the outcome of the decision is certain [147]. It is possible that an appropriate level of AI activity is necessary to provide an alerting signal that initiates brain responses to salient stimuli. If so, pathology could result from AI hyperactivity, as in anxiety, or hypoactivity, as might be the case in

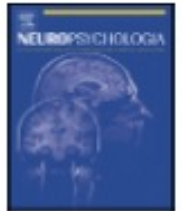
individuals is normal in the fusiform cortex, but not in the extended regions [152]. A decline in face perception with normal aging is also related to reduced structural integrity of the inferior fronto-occipital fasciculus [153].

### Conclusions and future directions

We have reviewed emerging methods for the identification and characterization of large-scale structural and functional brain networks, and have suggested new concepts in cognitive brain theory from the perspective of large-scale networks. Although critical open questions remain (Box 3), the large-scale brain network framework described here offers a principled and systematic approach to the study of cognitive function and dysfunction [154,155].

Continued progress in understanding of cognitive function and dysfunction will depend on the development of new techniques for imaging structural and functional brain connectivity, as well as new methods for investigating dynamic interactions within and between networks. In the remainder of this section, we discuss important directions for future research and highlight areas in which progress is likely to occur.

Although we have reviewed studies that tend to map cognitive functions onto large-scale brain networks, we expect that attempts to equate individual brain networks with a set of cognitive functions could prove to be just as inadequate as attempts to equate single brain regions with specific cognitive functions. It is likely that the function of any cognitive brain network ultimately depends on its multidimensional context [156]. We predict that future studies will explicitly recognize the importance of context in the formation of large-scale functional networks, and will seek to determine the other factors contributing to context in addition to anatomical structure.



# Attentional control: Temporal relationships within the fronto-parietal network

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Control of attention

## ABSTRACT

Selective attention to particular aspects of incoming sensory information is enabled by a network of neural areas that includes frontal cortex, posterior parietal cortex, and, in the visual domain, visual sensory regions. Although progress has been made in understanding the relative contribution of these different regions to the process of visual attentional selection, primarily through studies using neuroimaging, rather little is known about the temporal relationships between these disparate regions. To examine this, participants viewed two rapid serial visual presentation (RSVP) streams of letters positioned to the left and right of fixation point. Before each run, attention was directed to either the left or the right stream. Occasionally, a digit appeared within the attended stream indicating whether attention was to be maintained within the same stream ('hold' condition) or to be shifted to the previously ignored stream ('shift' condition). By titrating the temporal parameters of the time taken to shift attention for each participant using a fine-grained psychophysics paradigm, we measured event-related potentials time-locked to the initiation of spatial shifts of attention. The results revealed that shifts of attention were evident earlier in the response recorded over frontal than over parietal electrodes and, importantly, that the early activity over frontal electrodes was associated with a successful shift of attention. We conclude that frontal areas are engaged early for the purpose of executing an attentional shift, likely triggering a cascade through the fronto-parietal network ultimately, resulting in the attentional modulation of sensory events in posterior cortices.

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Despite the growing understanding of attentional selection gleaned from numerous studies, we do not yet have a full understanding of the mechanism that serves as the source to initiate the attentional orienting signal, which, ultimately, results in the neural modulation and behavioral benefit for attended locations. Investigations of this issue have uncovered a network of regions spanning frontal and parietal cortices that triggers a control signal for shifting from one representation to another, be it one that is space-based (Corbetta & Shulman, 2002; Hopfinger, Buonocore, & Mangun, 2000; Serences & Yantis, 2007), feature-based (Greenberg, Esterman, Wilson, Serences, & Yantis, 2010; Liu et al., 2003), or object-based (Shomstein & Behrmann, 2006). Although there is general consensus concerning regions that are engaged in this attentional shifting process, the relative contributions of the identified frontal and parietal regions have been difficult to characterize. Moreover, some studies have yielded conflicting findings, with several investigations suggesting that the initial spatial re-orienting signal is elicited by the frontal cortex, while others suggest that it is the parietal cortex that initiates the re-orienting signal with frontal cortex following suit (Brignani, Lepsien, Rushworth, & Nobre, 2009; Buschman & Miller, 2007; Green & McDonald, 2008; Simpson et al., 2011). It should be noted that while most investigations of bottom-up attentional capture have convincingly demonstrated that the shifting signal originates over the parietal cortex (Fu, Greenwood, & Parasuraman, 2005; Green, Doesburg, Ward, & McDonald, 2011; Hopfinger & Ries, 2005; Leblanc, Prime, & Jolicoeur, 2008; Ptak, Camen, Morand, & Schneider, 2011), most of the controversy regarding the temporal relationship between the source signals over frontal or parietal cortex has been exclusive to the investigations

By using a careful psychophysical method for determining the exact amount of time necessary for the initiation of a successful shift of spatial attention and by recording neural responses over the fronto-parietal attentional network, we were able to uncover the temporal relationship of neural processes underlying spatial shifts of attention. Our findings support several conclusions. Consistent with previous studies, we show that parietal and frontal cortices are involved in initiating the attentional shift (Brignani et al., 2009; Grent-'t-Jong & Woldorff, 2007; Moran & Desimone, 1985; O'Craven, Downing, & Kanwisher, 1999; Shomstein & Yantis, 2004; Simpson et al., 2011; Yantis et al., 2002). Moreover, we observed a highly structured temporal sequence of responses elicited following an intent to spatially re-orient attentional locus with attentional control signal first elicited by the frontal lobe and then followed by the parietal lobe. Needless to say, much remains to be done including further research to uncover the process by which the shift trigger is instantiated in frontal cortex, and to elucidate the mechanism by which this top-down cascade of shift signals is implemented. Electrophysiological techniques, extending beyond ERP to magneto-encephalography, offer great promise in this regard, and future explorations of long-range synchrony and frequency oscillations may help uncover the cortical dynamics, which ultimately underlie these processes.



# Dissecting the Brain's Internal Clock: How Frontal–Striatal Circuitry Keeps Time and Shifts Attention

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The ability of organisms to time and coordinate temporal sequences of events and to select particular aspects of their internal and external environments to which they will attend is vital to the organism's ability to adapt to the world around them. Numerous psychological theories have been proposed that describe how organisms might accomplish such stimulus selection and represent discrete temporal events as well as rhythm production. In addition, a large number of studies have demonstrated that damage to the frontostriatal circuitry appears to compromise the ability of organisms to successfully shift attention and behavior to adapt to changing temporal contexts. This suggests that frontostriatal circuitry is involved in the ability to make such shifts and to process temporal intervals. A selective review is accomplished in this article which focuses upon the specific neural mechanisms that may be involved in interval timing and set shifting. It is concluded that prefrontal cortex, substantia nigra pars compacta, pedunculopontine nucleus, and the direct and indirect pathways from the caudate to the thalamus may provide the neuroanatomical and neurophysiological substrates that underlie the organism's ability to shift its attention from one temporal context to another. 2001 Elsevier Science

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## Neuroimaging Evidence for Frontostriatal Circuitry Involvement in Interval Timing

Utilizing functional magnetic resonance imaging (fMRI), Hinton, Meck, and MacFall (1996) documented the first reported evidence for the involvement of the basal ganglia and frontal–striatal circuits in human interval timing. Participants performed in a peak-interval timing procedure (Rakitin et al., 1998) while brain scans were obtained. After controlling for both sensory-specific and motor effects, interval timing-related activation was demonstrated in the striatum, thalamus, and frontal cortex. Replicating this study, Meck, Hinton, and Mettall (1998) showed similar activa-

# Top-down modulation: bridging selective attention and working memory

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Selective attention, the ability to focus our cognitive resources on information relevant to our goals, influences working memory (WM) performance. Indeed, attention and working memory are increasingly viewed as overlapping constructs. Here, we review recent evidence from human neurophysiological studies demonstrating that top-down modulation serves as a common neural mechanism underlying these two cognitive operations. The core features include activity modulation in stimulus-selective sensory cortices with concurrent engagement of prefrontal and parietal control regions that function as sources of top-down signals. Notably, top-down modulation is engaged during both stimulus-present and stimulus-absent stages of WM tasks; that is, expectation of an ensuing stimulus to be remembered, selection and encoding of stimuli, maintenance of relevant information in mind and memory retrieval.

of sensory processing is not an intrinsic property of sensory cortices, but rather relies on long-range inputs from and interactions with a network of 'control' regions, including the prefrontal cortex (PFC) and parietal cortex [8,9]. We review evidence that a similar functional neural architecture of top-down modulation analogous to those that operate during perceptual analysis supports the prioritization of information in the service of WM.

In a typical visual WM task, participants are presented with an array of one or more items to be maintained in mind after the array is turned off over an interval of seconds (delay period) during which no stimulus information is present ('delayed-response' tasks). A single probe item or a probe array then appears, and the participant

## Glossary

**Selective attention:** goal-directed focus on one aspect of the environment.

*Special Issue: Cognition in Neuropsychiatric Disorders*

# Large-scale brain systems in ADHD: beyond the prefrontal–striatal model

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**Attention-deficit/hyperactivity disorder (ADHD) has long been thought to reflect dysfunction of prefrontal–striatal circuitry, with involvement of other circuits largely ignored. Recent advances in systems neuroscience-based approaches to brain dysfunction have facilitated the development of models of ADHD pathophysiology that encompass a number of different large-scale resting-state networks. Here we review progress in delineating large-scale neural systems and illustrate their relevance to ADHD. We relate frontoparietal, dorsal attentional, motor, visual and default networks to the ADHD functional and structural literature. Insights emerging from mapping intrinsic brain connectivity networks provide a potentially mechanistic framework for an understanding of aspects of ADHD such as neuropsychological and behavioral inconsistency, and the possible role of primary visual cortex in attentional dysfunction in the disorder.**

reasonable assumption that unexpected results probably represent false positives. However, accumulating evidence suggests that the prefrontal–striatal model of ADHD should be extended to include other circuits and their interrelationships from the perspective of systems neuroscience [10,11]. We suggest that formulation of a more inclusive brain model of ADHD is facilitated by the new paradigm of resting-state functional magnetic resonance imaging (R-fMRI), which is increasingly revealing the intrinsic functional architecture of the brain [12]. Finally, we speculate that modulation of neural networks through imaging-guided transcranial direct current electrical stimulation (tDCS) may provide novel therapeutic opportunities for disorders such as ADHD.

## **Resting-state functional magnetic resonance imaging**

Resting-state functional imaging, that is, imaging without a specific task (Box 1), is not new. It dates from the earliest



# Attention-Deficit/Hyperactivity Disorder and Attention Networks

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Research attempting to elucidate the neuropathophysiology of attention-deficit/hyperactivity disorder (ADHD) has not only shed light on the disorder itself, it has simultaneously provided new insights into the mechanisms of normal cognition and attention. This review will highlight and integrate this bidirectional flow of information. Following a brief overview of ADHD clinical phenomenology, ADHD studies will be placed into a wider historical perspective by providing illustrative examples of how major models of attention have influenced the development of neurocircuitry models of ADHD. The review will then identify major components of neural systems potentially relevant to ADHD, including attention networks, reward/feedback-based processing systems, as well as a 'default mode' resting state network. Further, it will suggest ways in which these systems may interact and be influenced by neuromodulatory factors. Recent ADHD imaging data will be selectively provided to both illustrate the field's current level of knowledge and to show how such data can inform our understanding of normal brain functions. The review will conclude by suggesting possible avenues for future research.

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## Cognitive Neuroscience Influences Relevant to ADHD Research

The field of cognitive neuroscience—with its search for the neurobiological substrates of component brain processes of cognition, attention, working memory, and motor control—has had an enormous effect on the current conceptualizations of ADHD. Although a detailed review comparing and contrasting different cognitive models, such as offered elsewhere (Posner, 2004), is beyond the scope of this paper, a few major influences on ADHD research can be identified.

One of the earliest and most influential cognition-related theories that attempted to explain selective attention was 'selection for action' (Allport, 1980, 1987; Posner and Petersen, 1990). This model sought to connect the modulation of attention and target identification with response selection. Specifically, it posited that attention would be selectively focused on target stimuli that were relevant to a response selection. Selection for action did not, however, require that an actual motor response be made, but could refer to an internally represented decision. Norman and Shallice (1986) referred to this form of attention as 'supervisory,' and suggested that it was used whenever processing of non-routine information was required. Furthermore, this form of attention was distinct from simple sensory orienting, and seemed to reflect a high level of cognitive control (Posner and Rothbart, 1998).

The review paper by Posner and Petersen (1990) on the attention system of the brain has been particularly influential. This model proposed that the 'attention system' was composed of three anatomically distinct but interacting network subsystems that influenced lower information processing modules. The three subsystems were those of orienting, detecting, and alerting/vigilance. Orienting referred to sensory processes such as visual foveation of a stimulus, and was proposed to rely on the parietal cortex, superior colliculus, and pulvinar/thalamus. The detection subsystem or 'anterior attention system' consisted of the anterior cingulate cortex (ACC) and lateral prefrontal cortex, and was posited to be responsible for detecting targets that would undergo further information processing. The alerting system, encompassing the noradrenergic locus coeruleus influences on mainly right hemisphere structures,

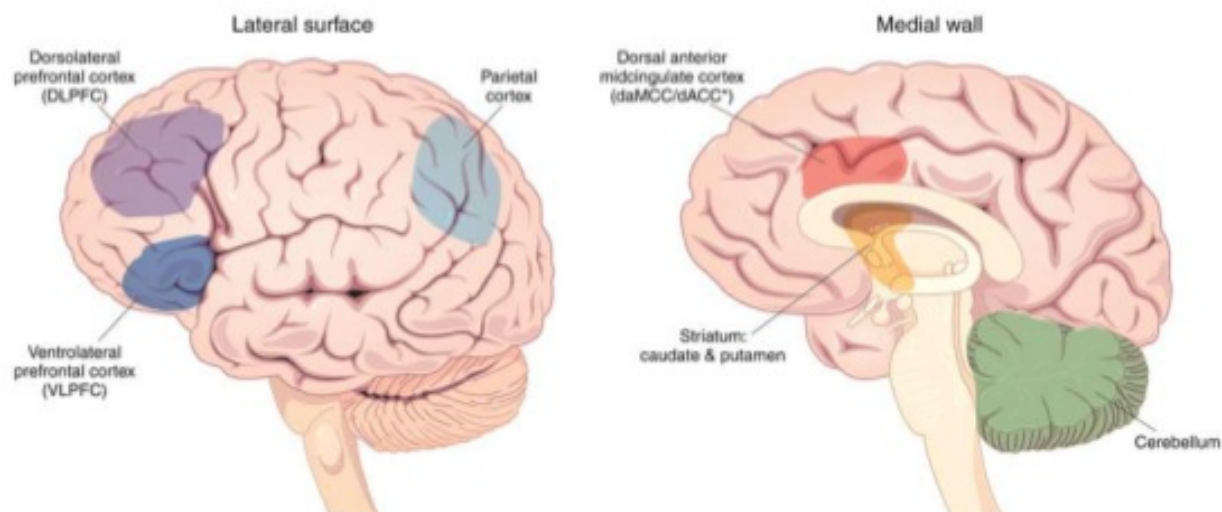
was responsible for maintaining general vigilance. Early PET studies on attention and vigilance by Pardo *et al* (1990) supported the framework of Posner and Petersen (1990): performance of a Stroop selective attention task-activated ACC, whereas a vigilance task-activated right lateral prefrontal and parietal cortex did not activate the ACC (Pardo *et al*, 1991). On the basis of, in part, this framework, Corbetta *et al* (1991) concluded that the ACC modulated the lower visual area activity during a divided attention task, and Raichle *et al* (1994) implicated the ACC as supporting novelty processing. Later, Corbetta (1998) and Corbetta *et al* (1998) expanded examination of these systems, identifying roles for frontal and parietal regions in attention. Together, these studies attempted to outline neurally plausible mechanisms for attention that stressed that regulation of subservient brain areas might depend on the degree of cingulo-fronto-parietal (CFP) activation. More recent functional imaging evidence has also supported Posner and Petersen's three-module framework and started to link these brain findings to genetic influences (Fan *et al*, 2003, 2005; Fan and Posner, 2004). Certainly, the selection-for-action influence (Holroyd, 2004), directly or indirectly, was evident in many subsequent papers involving a large variety of motor response selection tasks relevant to ADHD, including modality-specific motor choice (Paus *et al*, 1993), motor control/monitoring, and/or willed action (Badgaiyan and Posner, 1998; Liddle *et al*, 2001; Luu *et al*, 2000; Picard and Strick, 2001; Turken and Swick, 1999), Stroop and Stroop-like tasks (Bush *et al*, 1998; Pardo *et al*, 1990), and tasks involving the over-riding or inhibition of prepotent responses such as go/no-go, stop-signal, or countermanding tasks (Alderson *et al*, 2007; Aron *et al*, 2003; Durston *et al*, 2003a; Ito *et al*, 2003; Kawashima *et al*, 1996). Although lacking in the full, necessary precision desired for a complete mechanistic account of attention, selection for action helped pave the way for studies trying to link brain processes with attention and ADHD.



### CFP Attention Network

On the basis of these studies and the wider cognitive neuroscience literature, imaging studies attempting to identify the pathophysiology of ADHD logically searched for abnormalities of brain regions that are normally involved in attention, cognition, executive function, motor control, response inhibition, working memory, and/or reward/motivation. As detailed below, this line of thinking led researchers to gravitate toward studies on the dorsal anterior midcingulate cortex (daMCC), dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and parietal cortex. Although the cingulate cortex nomenclature has been revised as the field has matured, it is noted here that the term 'daMCC' refers to essentially the same region of the cingulate cortex that was referred to previously as the ACC or as the dorsal ACC in many contemporary references (Bush, 2009; Vogt, 2005; Vogt *et al*, 1992). Together, these regions comprise the main





**Figure 1.** Brain structures implicated in ADHD. Interacting neural regions have been implicated in ADHD. In particular, the dorsal anterior midcingulate cortex (daMCC), dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), parietal cortex, striatum, and cerebellum—all key elements of cognitive/attention networks—have also been found to display functional abnormalities in multiple studies of ADHD.

#### ADHD and attention networks

G Bush

Resting state studies. Although the majority of functional imaging studies have concentrated on using various cognitive activation paradigms to specifically target different elements of the neural circuits subserving cognition, attention, and motor functions, growing interest has been noted in the use of techniques that focus on subjects' resting brain activity. Such resting studies are important as one of the main problems in ADHD may lie in dysfunction of brain regions that, as discussed above, support a proposed 'default network'. Specifically, it may be the case that an abnormally high default mode network activity may interfere with CFP attention network activity.

Neuropsychopharmacology **REVIEWS**

One resting state PET study showed that MPH increased rCBF in the cerebellar vermis and was associated with decreased rCBF in the precentral gyri, caudate, and claustrum (Schweitzer *et al*, 2003), whereas another reported MPH potentiates dopaminergic activity in the striatum of adolescents with ADHD (Rosa-Neto *et al*, 2005). A series of resting state MRI studies has also provided insights into functional connectivity among brain regions, primarily fronto-cingulate-cerebellar circuits (Tian *et al*, 2006; Zang *et al*, 2006; Zhu *et al*, 2005). Later, resting state discriminative analysis indicated dysfunction of the daMCC, lateral prefrontal cortex, thalamus, and lateral parietal cortex in ADHD (Zhu *et al*, 2008), whereas Tian *et al* (2008) used resting state MRI to show that ADHD patients exhibited higher resting state activity in the lower-level sensory cortex, concluding that this was related to inattention. Interestingly, Castellanos *et al* (2008) identified reduced functional connectivity between the daMCC and default network structures (precuneus and PCC) and altered connectivity within default network itself (VMPFC, precuneus, and PCC)—findings that were essentially confirmed by the same group using a different network homogeneity model (Uddin *et al*, 2008). Work in this vein has been based on hypothesized interruption of attention network activity by altered default network activity (Weissman *et al*, 2006), which in ADHD has been thought to lead to greater variability in ADHD performance (Sonuga-Barke and Castellanos, 2007). ASL techniques, which can provide absolute measures of rCBF during rest (Aguirre *et al*, 2002; Detre and Wang, 2002; Kim *et al*, 2006; Wang *et al*, 2005) should help better define the pathophysiology of ADHD and



possible new avenues of research.

*Resting state studies.* Resting functional connectivity studies have recently formed a major trend in ADHD research and can provide valuable new information. Greater efforts to directly link such connectivity data with fMRI attention task and DTI connectivity data will be helpful. More importantly, the use of ASL techniques (Aguirre *et al*, 2005; Detre and Wang, 2002), which can provide absolute, as opposed to relative, measures of resting state brain activity, will be crucial to defining the relationships between cognitive, vigilance, and emotional circuits. Such ASL studies would provide uniquely important data not available from typical fMRI data sets nor resting state connectivity studies. Specifically, ASL studies would allow testing of the hypothesis that abnormally high default network activity interferes with normal CFP attention network activity in ADHD—a hypothesis suggested and supported by the study of Weissman *et al* (2006) and Sonuga-Barke and Castellanos (2007).

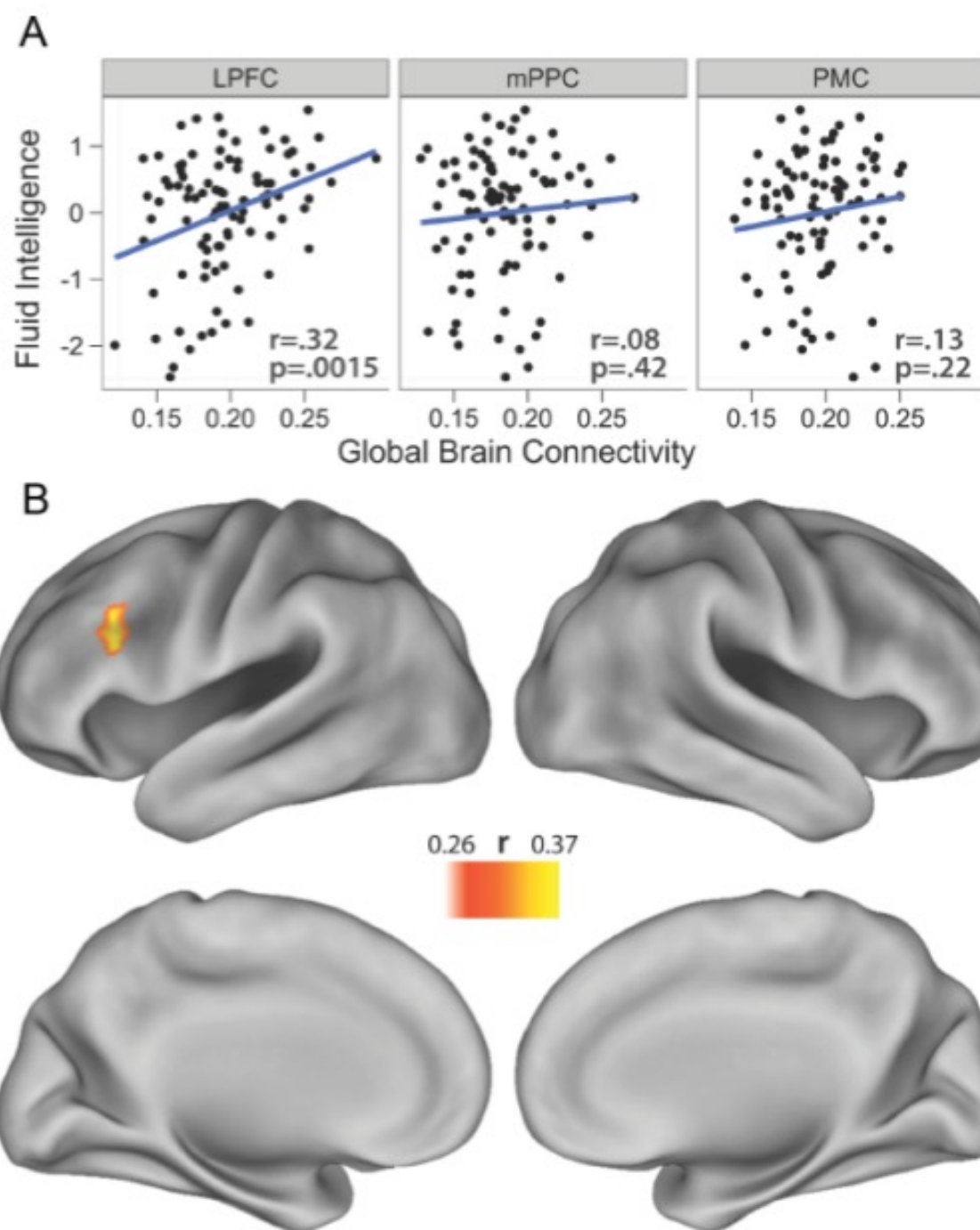
# Global Connectivity of Prefrontal Cortex Predicts Cognitive Control and Intelligence

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Control of thought and behavior is fundamental to human intelligence. Evidence suggests a frontoparietal brain network implements such cognitive control across diverse contexts. We identify a mechanism—global connectivity—by which components of this network might coordinate control of other networks. A lateral prefrontal cortex (LPFC) region's activity was found to predict performance in a high control demand working memory task and also to exhibit high global connectivity. Critically, global connectivity in this LPFC region, involving connections both within and outside the frontoparietal network, showed a highly selective relationship with individual differences in fluid intelligence. These findings suggest LPFC is a global hub with a brainwide influence that facilitates the ability to implement control processes central to human intelligence.





**Figure 2.** GBC correlations with gF. **A**, Positive GBC was calculated for the 3 regions identified in the task-based analysis, and correlations were assessed with gF. Only LPFC showed a significant correlation. GBC is a graph theoretical measure of resting state fMRI, calculated here for each seed ROI, by computing the average connectivity strength between the region and every other voxel of the brain. Note that all 3 regions were in the top 10% in terms of GBC (but only LPFC GBC was significantly correlated with gF). **B**, Correlations were assessed between each brain voxel's positive GBC and gF scores. Of the entire brain, only left LPFC was statistically significant ( $p < 0.05$ , corrected for multiple comparisons). The LPFC region strongly overlapped with the LPFC region identified in the task-based analysis.





### **Theoretical implications and future directions for research**

In contrast to studies emphasizing whole-brain network contributions to intelligence or studies emphasizing the contributions of specific regions (or networks) to intelligence, we found that a specific region's global connectivity predicts intelligence. This suggests a reconceptualization of LPFC as a **functional hub** that uses its brainwide influence to facilitate cognitive control and intelligence. Importantly, the observation of other cognitive control regions with high GBC but significantly lower GBC–gF correlations suggests that LPFC likely has some additional properties beyond extensive connectivity that underlie the observed GBC–gF correlation.

One possibility, based on Miller and Cohen's (2001) model of LPFC function, is that LPFC acts as a "flexible" hub, able to flexibly shift its connectivity with a variety of task-relevant regions according to task demands. Within this conceptualization, resting state fMRI GBC likely reflects the number of possible routes that LPFC can use during tasks to reconfigure connectivity. Thus, individuals with greater LPFC GBC would likely be able to dynamically reconfigure to a more specific connectivity pattern for any of a wide variety of possible task demands, increasing the specificity of LPFC's control over activity in those regions. This increased capacity for control across individuals would likely be reflected in the LPFC GBC–gF correlation. Further research is necessary to verify other predictions of the flexible hub hypothesis, such as task-dependent shifts in connectivity [but see Rowe et al. (2005), Cole et al. (2010a), Stelzel et al. (2011), and Deserno et al. (2012)].

We found that the LPFC GBC–gF correlation was present across a wide variety of strength ranges and spatial locations. Supporting the flexible hub account, many of these connections were with sensory and motor regions. This may reflect a particular architecture for a flexible neural system underlying human intelligence: Engineers have characterized flexible, adaptive control in terms of the ability for a system to access (both monitor and influence) multiple sources of task-relevant information (Åström and Murray, 2008). Additionally, although the functional importance of negative connectivity is not well understood (Murphy et al., 2009), the predictive relationship between gF and LPFC connections with the default mode network is consistent with a key role for inhibition of task-irrelevant processing in cognitive control and fluid intelligence (Anticevic et al., 2010). Further investigation into the functional relevance of cognitive control hubs, including the possibility that LPFC benefits from high global connectivity due to its unique flexibility, will be essential for understanding the neural architecture underlying human intelligence.